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ORIGINAL ARTICLE

Straightforward synthesis of pyrimido[4,5-*e*][1,4]diazepines *via* 6-aminopyrimidin-5-carbaldehydes

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KEYWORDS

4(6)-Aminopyrimidines;
Diazepines;
Fused heterocycles;
Acylation;
Cyclization

Abstract A high-throughput method to obtain several pyrimido[4,5-*e*][1,4]diazepines is described by a two-step acylation/cyclization sequence from key intermediates 6-amino-5-(amino)methylpyrimidines, which were prepared from the precursor 6-aminopyrimidin-5-carbaldehydes. The acylation is accomplished with haloacyl halides to render ((4-aminopyrimidin-5-yl)-methyl)-2-haloamide intermediates. The cyclization step worked successfully, but depending on the substituents, competitive reactions *versus* the cyclization to pyrimido[4,5-*e*][1,4]diazepines were found to afford indolinones or acrylamides which were formed *via* alternative cyclization or elimination respectively. The pyrimido[4,5-*e*][1,4]diazepines were derivatized by alkylation at N(9), and a two-step one-pot procedure, cyclization/alkylation, from the ((pyrimidin-5-yl)-methyl)-2-haloamide intermediates was optimized to the formation of these N(9)-substituted derivatives.

1. Introduction

The benzodiazepine system has been described as a privileged structure due to the ability of compounds with such frame to link to multiple biological receptors (Costantino and Barlocco, 2006; Horton et al., 2003). On the other hand, pyrimidine-fused compounds are of interest in medicinal chemistry and chemical biology due to their wide range of biological activities (Sagar et al., 2015; Dinakaran et al., 2012; Wang et al., 2004; McGuigan et al., 2004; Gangjee et al., 2004). The fusion of pyrimidine and diazepine rings will result in purine/pteridine mimicking bicyclic scaffold, which has attracted the chemists' attention for many years (Freidinger et al., 1992; Di Braccio et al., 2001; Schaefer et al., 1981; Kobayashi, 1974, 1975). Pyrimidodiazepines have been reported for a wide range of biological applications (see Fig. 1) such as in the treatment of different disorders *via* inhibition of phenylalanine hydroxylase (Pike et al., 1986), Aurora A kinase (Kanhed et al., 2015), tyrosine kinase (**A**) (Gracias et al., 2008) or EGFR (Xu et al., 2012), having immunosuppressive activity (**B**) (Dlugosz, 1998) with properties such as anticonvulsant (Kim and Santilli, 1969; Murthy and Knaus, 1999) antipyretics, (Juby and Hudyma, 1974) or gastric secretion inhibitors (**C**) (Dlugosz, 1990), or prepared as second generation of ß-secretase modulators (**AZ1136**) (Borgegard et al., 2012).

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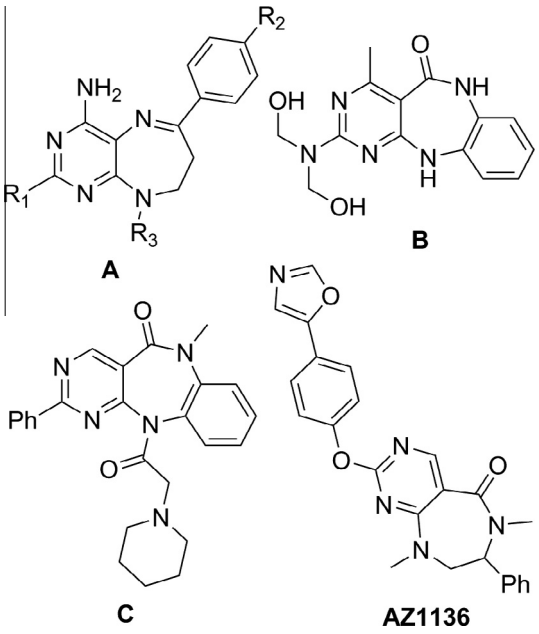


Figure 1 Examples of bioactive pyrimidodiazepines.

The most common pyrimidodiazepine system described in the literature is the pyrimido[4,5-*b*][1,4]diazepine such as **A** (see Fig. 1). Regarding these derivatives, we have already reported the synthesis of diverse compounds and tested their biological applications. Most of them have been prepared from 4,5-diaminopyrimidines by reaction with biselectrophilic reagents such as chalcones (Insuasty et al., 2008, 2010, 2014) or from 6-methoxy-5-nitrosopyrimidines in a three step sequential methodology: aromatic nucleophilic substitution/reduction/cyclocondensation (Marchal et al., 2002, 2010; Cobo et al., 2008).

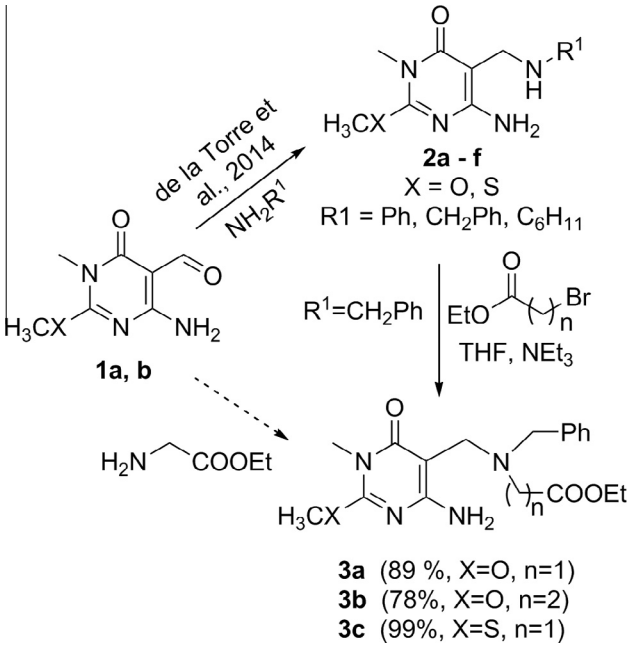
As we are interested in exploring the non-common pyrimido[4,5-*e*][1,4]diazepine system as an interesting biological target scaffold like those shown in Fig. 1, we describe the synthesis of a novel series of those derivatives focused on the 6-aminopyrimidine-5-carbaldehydes as key precursors in a high-throughput methodology, as an alternative to the preparation of pyrimido[4,5-*e*][1,4]diazepin-7-ones reported by a sequence of five steps starting from 4,6-dichloropyrimidin-5-carbaldehyde using α-aminoesters and primary amines (Xiang et al., 2010). Our approach consists of four-step process initially starting from the corresponding 6-aminopyrimidines, that includes a formylation reaction followed by condensation with amines rendering the intermediates 6-amino-5-(amino)methylpyrimidines and finally an acylation/cyclization sequence in reaction with haloacyl derivatives. This is an extension of the previous work reporting the synthesis of 6-amino-5-(amino) methyl pyrimidines by reductive amination from their corresponding pyrimidin-5-carbaldehyde derivatives that were used as key intermediates to pyrimidopyrimidine derivatives (de la Torre et al., 2014).

2. Results and discussion

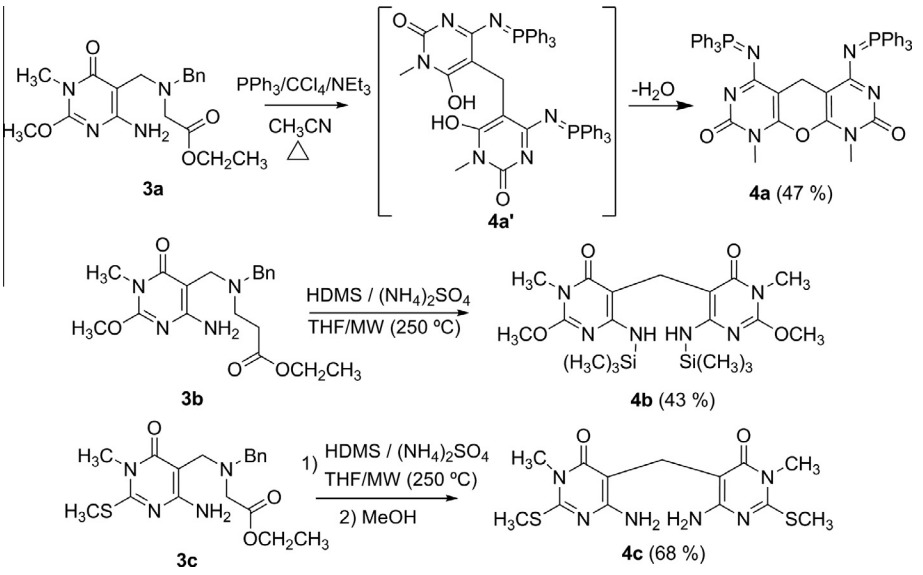
Our first approach, to reach the target pyrimidodiazepines, was by the reaction of the precursor 6-aminopyrimidin-5-carbaldehydes **1a,b** with aminoesters. Likewise to the building of the diazepine ring from 2-aminobenzaldehydes, we tried different conditions and/or reduction agents in order to perform condensation or reductive amination reactions in compounds **1**. A failure of those reactions could be explained in regard to the lesser reactivity of both 6-amino and aldehyde in the pyrimidine system than in benzene. Next, we carried out the reaction of the 6-amino-(5-aminomethyl)pyrimidines **2a–f** (de la Torre et al., 2014) with α- and β-bromoesters in a polar solvent (DMF) and using a base (potassium carbonate) as promoter. It afforded the desired intermediates **3** which were isolated nearly quantitative yields (see Scheme 1). Unfortunately, all the attempts of cyclization of intermediates **3** to pyrimidodiazepines did not work. Hence we tried acid (HOAc, PTSA, TFA) and base (NaOH, NaOEt, K_2CO_3) catalysis, microwave irradiation and fusion which led to the decomposition of the starting material observed in most of these reactions.

Thereafter, we decided to increase the nucleophilicity of the 6-amino group by formation of the corresponding silyl or phosphorane intermediates, but the desired cyclized derivatives were not formed. The absence of the corresponding ester (or amide if cyclized) moiety in the spectroscopic data was not observed. Instead of that, the analysis of the NMR and MS spectra indicated the formation of the methylene bispyrimidin-5-yl derivatives **4** (see Scheme 2 and experimental for interpretation). It seems that secondary amino linked to 5-methylenepyrimidine is also attacked by the silyl or phosphine reagents, leading to the formation of cationic intermediates that caused the cleavage of a bond around methylene residue, *via* α or β cleavage with respect to the amino group resembling elimination/addition found in the equilibria of asymmetric aminals as compounds **3** can be considered like phenylogous aminals. In the case of **4a**, in addition to the formation of the methylene bispyrimidin-5-yl derivative, a demethylation and cyclization take place in the formation of this compound.

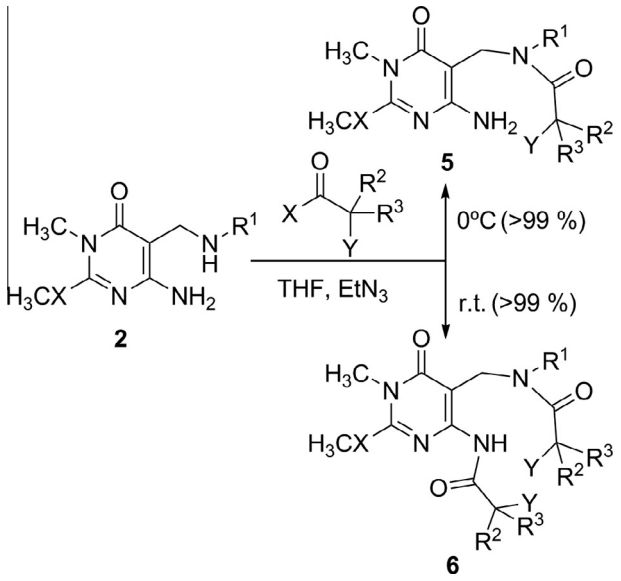
Because of the above unfruitful results, we used the classical haloacyl halides as biselectrophilic reagent to accomplish our target, which reacted with diaminopyrimidine intermediates **2** to afford the corresponding amide intermediates **5** in yields > 99%, in only 5 min at 0 °C using THF as solvent in the presence of triethylamine (see Scheme 3 and Fig. S1 in supporting information). When the reaction was carried out at room tem-



Scheme 1 Synthesis of the (4-aminopyrimidin-5-yl)methylamino ester intermediates **3**.



Scheme 2 Results arisen from attempts of cyclization *via* compounds **3** to yield 5,5′-methylenebispyrimidines (**4**).



Scheme 3 Synthesis of the halo-amide derivatives **5** used as intermediates.

perature or with some excess of the 2-haloacyl halide the corresponding bisamide derivatives **6** were obtained. In addition to the usual spectroscopic characterization of compounds **5**, where the new signals corresponding to the haloacyl moiety are observed (see Tables S3 and S4 in supporting information for a complete assignation of NMR spectra), the structure of derivative **5i** was solved by single crystal X-ray diffraction (see Fig. 2), in which the intramolecular hydrogen bond between 4-amino group and the oxygen of amide residue is shown.

It has to be noted that in the case of the reaction of **2a** (R^1 = phenyl) with 2-chloro-2,2-diphenylacetyl chloride, we have found that instead of the expected chloroacetamide **5a′**, an intramolecular Friedel-Craft cyclization took place to afford hybrid compound **7** (Scheme 4). This is explained by

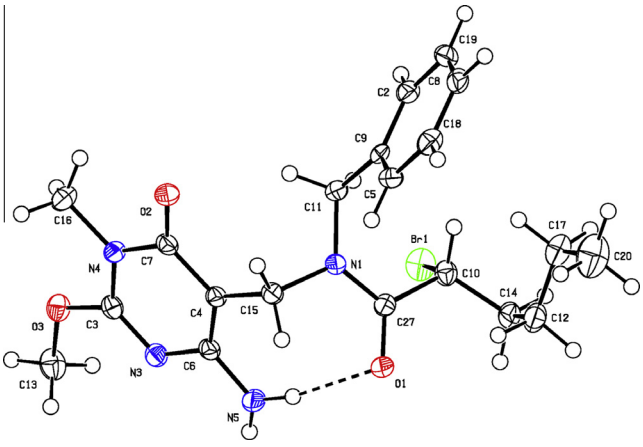
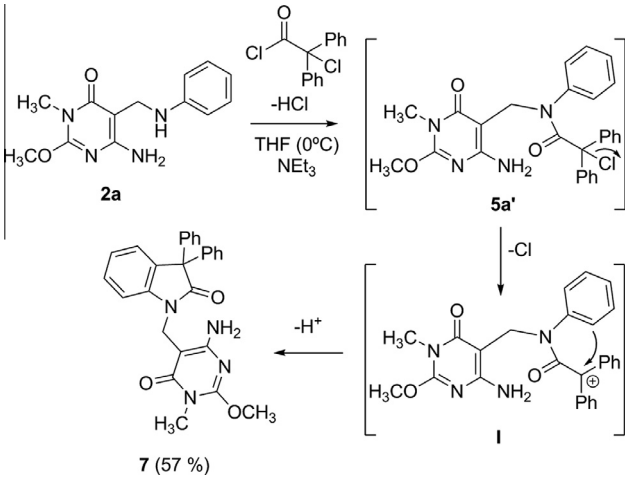


Figure 2 ORTEP drawing of the structure **5i** with 50% probability ellipsoids.



Scheme 4 Synthesis of the indoline derivative (**7**).

means of the formation of the carbocation at α position of carbonyl group, species **I**, which is stabilized by the two attached phenyl groups, which is then attacked by the activated phenyl ring linked to nitrogen.

This compound **7** is characterized by the observation in its ^{1}H NMR spectrum of the typical coupling system found in ortho disubstituted benzene moieties (see experimental for signal interpretation), and in its ^{13}C NMR spectrum the downshielded displacement of the signal C═O in the five member ring in this new indolinone residue, at 179. 8 ppm, in respect of the open related compounds **5g** and **5t** (in this R^1 = benzyl) at 171.5 ppm can be observed. A similar effect is found in the corresponding IR signal for the C═O group, with an increase of 15–20 cm^{-1} with respect to the related compounds **5g** and **5t**, in agreement to the formation of the new five member ring.

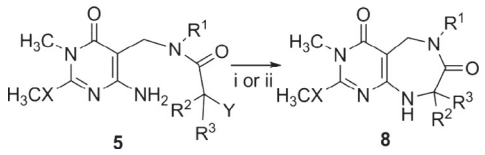
In order to build the diazepinic nucleus, compounds **5** were heated at 80-90 °C in DMF with potassium carbonate as promoter, to afford the desired pyrimidodiazepines **8** in good to excellent yields (see table in Scheme 5). When sodium hydride was used as a promoter at room temperature the reaction is 5–60 times quicker with simpler work-up and without need of chromatographic purification.

Compounds **8** were fully characterized by the standard spectroscopic methods (see Tables S5 and S6 in supporting information for full assignation of NMR spectra). The cyclization was confirmed by ^{1}H NMR due to the coupling of hydrogen at N(9) with H-8 and if $R^2 \neq H$ the two hydrogens at C(5) became diastereotopic and also because in some cases HMBC correlation between hydrogen at N(9) and C(8) was observed. In addition, the structure of compound **8u** was unambiguously confirmed by single crystal X-ray diffraction, which is displayed in Fig. 3.

We have to note that in some derivatives where R^2 = Ph; R^3 = H (**5c, 5p, 5s, 5y**) or R^2 = R^3 = Ph (**5g, 5m, 5t**) the cyclization merges with decomposition which could explain the problems with reproducibility observed for those reactions. As depicted in Scheme 4, a stabilized carbocation can be formed favorably in polar solvent (DMF) such as the one used in the reaction can evolve in many different ways, such as the one leading to **7** because of the low nucleophilicity of 6-amino group.

In the case of steric hindered derivative **5j**, the treatment with the base gave rise to elimination rather than intramolecular nucleophilic substitution and therefore affording acrylamide derivative **9a** (see Scheme 6). The acrylamide residue is observed in the ^{1}H NMR spectra appearing the two geminal alkenyl H as broad singlets in the ^{1}H NMR at 5.07 and 5.12 ppm, and the two new signal for the alkenyl in the ^{13}C NMR at 115.4 (CH_2) and 137.5 (see Tables S7 and S8 in supporting information for a full interpretation of NMR spectra). However this compound **9a**, in turn, could be a good precursor to pyrimidodiazocine system. Unfortunately the attempts to perform such cyclization were unsuccessful. A similar behaviour was observed for R^2 alkyl substituents that could explain the low yield for **8h** (R^2 = Et), or the lack of reproducibility of some reactions when running with NaH.

Considering the good results afforded for the preparation of pyrimidodiazepines **8**, we have also postulated the preparation of pyrimidodiazocine system in a similar fashion. Some diaminopyrimidine compounds type **2** were treated with β-haloacyl halides, as shown in Scheme 7, resulting in the corresponding amides **10a–c**. In addition to the spectroscopic



Entry[a]	X	R^1	R^2	Y	Reaction yields for 8 (%)[i]	(%)[ii]
a	O	Ph	H	Cl	84	98
b	O	Ph	CH_3	Cl	85	58
d	O	Bn	H	Cl	70	84
e	O	Bn	CH_3	Cl	64	88
f	O	Bn	Ph	Cl	64	82
h	O	Bn	C_2H_5	Br	38	[a]
i	O	Bn	C_4H_9	Br	55	95
k	O	C_6H_{11}	H	Cl	75	57
l	O	C_6H_{11}	CH_3	Cl	62	90
n	S	Ph	H	Cl	70	64
o	S	Ph	CH_3	Cl	90	94
q	S	Bn	H	Cl	80	77
r	S	Bn	CH_3	Cl	84	86
s	S	Bn	Ph	Cl	87	[b]
u	S	Bn	C_2H_5	Br	91	[b]
v	S	Bn	C_4H_9	Br	93	[b]
w	S	C_6H_{11}	H	Cl	56	57
x	S	C_6H_{11}	CH_3	Cl	90	88
y	S	C_6H_{11}	Ph	Cl	[b]	90

[a] Starting Material **5** (R^3=H; but **5g** R^3=Ph); Some phenyl (R^2) derivatives (**5c,g,m,p** and **t**) are not included because gave problems with reproducibility in the cyclization step.

[b] Problems with reproducibility.

Scheme 5 Cyclization of intermediates **5** to pyrimidin[4,5-*e*][1,4]diazepines (**8**). Yields under conditions i: K_2CO_3, DMF, 90 °C; ii: NaH, DMF, room temperature.

characterization, we have also performed a single crystal X-ray diffraction analysis on compound **10a**, structure of which is shown in Fig. 4. Accordingly, these amides **10a–c** were treated with base for the corresponding cyclization, but instead they accomplished formation again of acrylamide derivatives type **9b,c**, showing similar spectroscopic characteristics as previously described for **9a**. This elimination reaction is favored by the acid character of hydrogen at β position with respect to the halogen in the basic media.

Further transformations of these pyrimido[4,5-*e*]diazepine **8** can be done in order to increase the diversity, such as $N_{(9)}$ alkylation, aminolysis through methylthio group after oxidation, debenzylation. Here we present the methylation of $N_{(9)}$ carried out using methyl iodide as alkylating agent in DMF and in the presence of NaH as base. A total of six pyrimido

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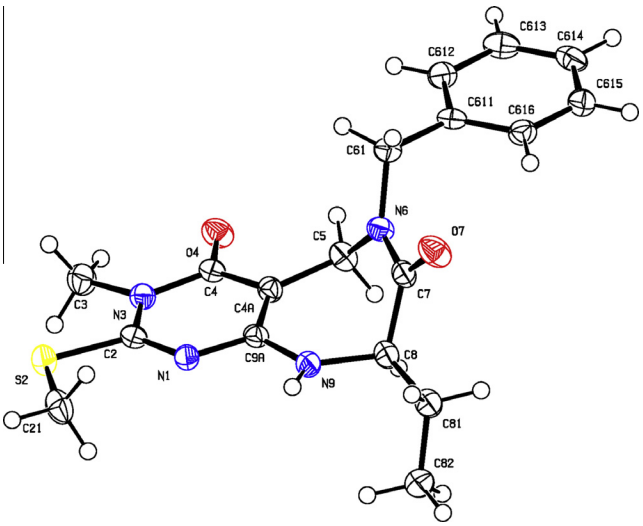


Figure 3 ORTEP drawing of the structure **8u** with 50% probability ellipsoids.

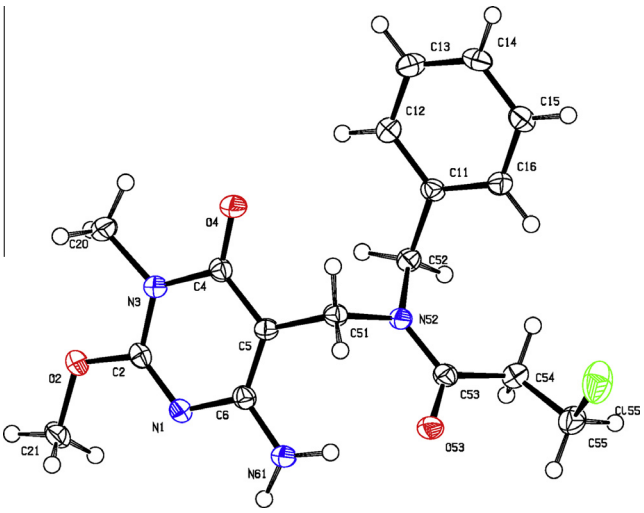
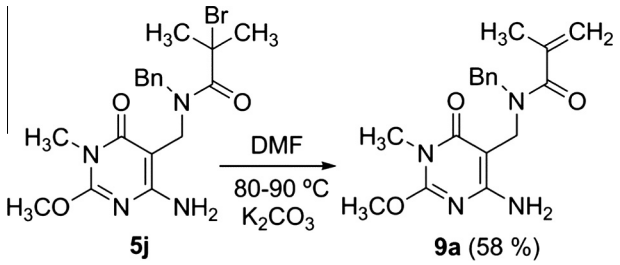
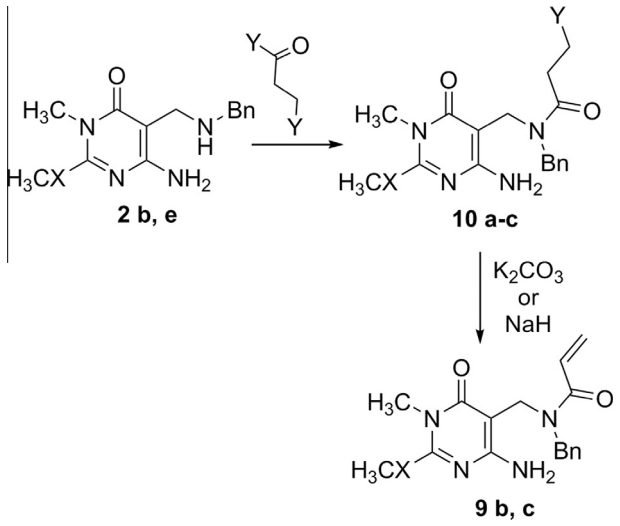


Figure 4 ORTEP drawing of the structure **10a** with 50% probability ellipsoids.

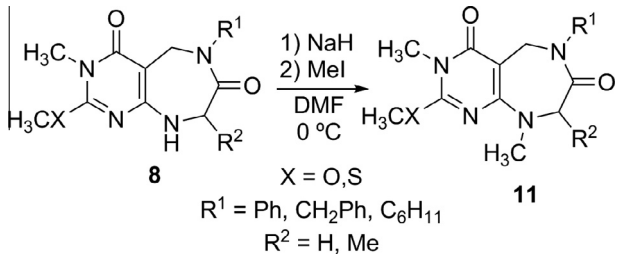


Scheme 6 Elimination reaction in the steric hindered derivative **5j**.



Scheme 7 Reaction pathway to the acrylamide derivatives from compounds **10**.

[4,5-*e*]diazepines **11** have been prepared (see Scheme 8) and completely characterized (Tables S9 and S10 in supporting information for a full interpretation of NMR spectra), including solution of crystalline structure of **11f** by single crystal X-ray diffraction (Fig. 5).



Scheme 8 Methylation at N(9) of some pyrimido[4,5-*e*][1,4]diazepines.

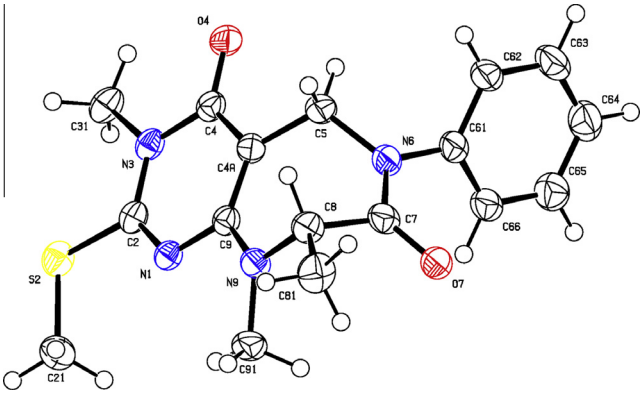


Figure 5 ORTEP drawing of the structure **11f** with 50% probability ellipsoids.

Because both the solvent and the base used for both cyclization and methylation processes are the same, the corresponding one-pot tandem two-step reaction from the amide intermediates **5** towards the final methylated derivatives **11a–f** was tried and resulted successfully in similar global yield to slightly higher than doing the two reactions.

Due to the attractive biological potential of intermediates **5** and pyrimidodiazepine **8** preliminary biological assays have been carried out, including antimicrobial with pathogenic fungi and bacteria, antiviral or antitumoral activities, but up to this moment we have not obtained any positive results.

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3. Conclusions

We have developed a simple and straight-forward three-step procedure to obtain several pyrimido[4,5-*e*][1,4]diazepines starting from 6-amino pyrimidin-5-carbaldehydes, consisting of a reductive amination to intermediates 6-amino-5-(amino)methylpyrimidines and an acylation/-cyclization sequence in reaction with haloacyl derivatives. In the reaction to reach cyclized derivatives we have also found the hybrid indolinone or acrylamide derivatives formed by competitive routes, that is, an alternative cyclization or elimination respectively, opening a synthetic way to obtain those interesting hybrids. Derivatization of these pyrimido[4,5-*e*][1,4]diazepines is easily accomplished through the N(9) position without need of isolation from cyclization step.

4. Experimental

Melting points were determined on a *Barstead Electrothermal 9100* melting point apparatus and are uncorrected. IR spectra were recorded in KBr discs on *Bruker TENSOR 27* spectrophotometer from "Centro de Instrumentación Científico-Técnica (CICT) at Universidad de Jaén". ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (CICT) operating at 400 MHz and 100 MHz respectively, using $CDCl_3$ and [D_6]DMSO as solvents and tetramethylsilane as internal standard; the carbon type described p (primary), s (secondary), t (tertiary) and q (quaternary) at ^{13}C NMR was deduced from DEPT-135 and 2D-NMR experiments. Mass spectra were run on a SHIMADZU-GCMS 2010-DI-2010 spectrometer (equipped with a direct inlet probe) operating at 70 eV. High resolution Mass spectra were run on a *Waters Micromass AutoSpec-Ultima* spectrometer (equipped with a direct inlet probe) operating at 70 eV. Silicagel aluminium plates (Merck 60 F_{254}) were used for analytical TLC. Silicagel 60 (35–70 μm) purchased from Merck was used for flash column chromatography. The microwave assisted reactions were carried out in a focused mono-mode microwave oven apparatus ("Discover" by CEM Corporation) using 10 ml glass sealed tubes and working at standard mode by controlling the target temperature. The starting amines and haloacyl derivatives were purchased from Aldrich, Fluka and Acros (analytical reagent grades) and were used without further purification.

4.1. Preparation of intermediates (4-aminopyrimidin-5-yl) methylamino esters

To a solution of 6-amino-5-((substituted-amino)methyl)pyrimi din-4(3H)-one **2** (1 mmol) in DMF (2 mL), a suspension of potassium carbonate (0.2 g, 1.5 mmol) in water (2 mL) is added and stirred for 10 min and then the corresponding haloester (2 mmol) is added drop-wise to the above white paste. The reaction mixture was stirred for the appropriate time until the compound **2** was not detected by TLC (eluent DCM/MeOH, 9:1). When reaction finished 10 ml of water was poured into the solution and a colourless solid was formed, which was filtered and washed with water.

*4.1.1. Ethyl-2-{[(4-amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl](benzyl)amino}acetate (**3a**)*

From 0.274 g of *6-amino-5-((benzylamino)methyl)-2-meth oxy-3-methylpyrimidin-4(3H)-one* **2b** and 0.3 ml of ethyl bromoacetate. Reaction time: 3 h. Yield: 89%. M.p. 108 – 9 °C. ^{1}H NMR (DMSO-d_6). δ_{ppm}: 1.15 (t, 7.0 Hz, 3H); 3.13 (s, 2H); 3.16 (s, 3H); 3.43 (s, 2H); 3.46 (s, 2H); 3.88 (s, 3H); 4.06 (q, 7.0 Hz, 2H); 6.74 (bs, 2H); 7.20–7.29 (m, 5H). ^{13}C NMR (DMSO-d_6) δ_{ppm}: 13.9 p; 27.0 p; 48.8 s; 54.0 s; 55.0 p; 56.1 s; 60.3 s; 85.9 q; 126.85 t; 128.1 t; 128.6 t; 138.9 q; 155.4 q; 160.4 q; 162.1 q; 171.8 q. IR (KBr) ν (cm^{-1}): 3398 (s); 3331 (m); 3228 (m); 3060 (w); 3028 (w); 2954 (w); 2845 (w); 1739 (s); 1634 (s, b); 1544 (s, b); 1487 (m). MS (70 eV) *m*/*z* (%): 360 (M^+, 0.3), 269 (53); 192 (48); 168 (100); 120 (28); 106 (14); 91 (85). HR MS: calc for $C_{18}H_{24}N_4O_4$ 360.1798; found 360.1802.

*4.1.2. Ethyl-3-{[(4-amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl](benzyl)amino}propanoate (**3b**)*

From 0.274 g of **2b** and 0.3 ml of ethyl bromopropionate. Reaction time: 16 h. Yield: 78%. M.p. 125 – 7 °C. ^{1}H NMR (DMSO-d_6). δ_{ppm}: 1.10 (t, 7.0 Hz, 3H); 2.45 (t, 6.8 Hz, 2H); 2.59 (t, 6.8 Hz, 2H); 3.16 (s, 3H); 3.37 (s, 2H); 3.43 (s, 2H); 3.87 (s, 3H); 3.96 (q, 7.0 Hz, 2H); 6.27 (bs, 2H); 7.21–7.30 (m, 5H). ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.16 (t, 7.0 Hz, 3H); 2.49 (t, 6.8 Hz, 2H); 2.78 (t, 6.8 Hz, 2H); 3.31 (s, 3H); 3.52 (s, 2H); 3.56 (s, 2H); 3.92 (s, 3H); 4.02 (q, 7.0 Hz, 2H); 5.51 (bs, 2H); 7.21–7.30 (m, 5H). ^{13}C NMR (DMSO-d_6) δ_{ppm}: 13.9 p; 27.0 p; 31.6 s; 48.2 s; 48.8 s; 55.0 p; 56.9 s; 59.8 s; 86.1 q; 126.7 t; 128.0 t; 128.8 t; 139.2 q; 155.3 q; 160.2 q; 162.0 q; 172.2 q. ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.0 p; 27.5 p; 32.6 s; 48.8 s; 49.6 s; 55.1 p; 57.9 s; 60.35 s; 88.3 q; 126.9 t; 128.2 t; 129.1 t; 139.4 q; 155.7 q; 160.3 q; 163.25 q; 172.9 q. IR (KBr) ν (cm^{-1}): 3448 (m); 3311 (m); 3199 (w); 3027 (w); 2977 (w); 2835 (w); 1727 (s); 1640 (s); 1621 (s); 1548 (s). MS (70 eV) *m*/*z* (%): 283 (57); 206 (100); 168 (72); 120 (25); 106 (41); 91 (95). HR MS: calc for $C_{19}H_{26}N_4O_4$ 374.1954; found 374.1955.

*4.1.3. Ethyl-2-{[(4-amino-1-methyl-2-methylthio-6-oxo-1,6-dihydropyrimidin-5-yl)methyl](benzyl)amino}acetate (**3c**)*

From 0.290 g of *6-amino-5-((benzylamino)methyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one* (**2e**) and 0.3 ml of ethyl bromoacetate. Reaction time: 4 h. Yield: 99%. M.p. 109 – 10 °C. ^{1}H NMR (DMSO-d_6). δ_{ppm}: 1.17 (t, 7.0 Hz, 3H); 2.52 (s, 3H); 3.15 (s, 2H); 3.30 (s, 3H); 3.47 (s, 2H); 3.49 (s, 2H); 4.08 (q, 7.0 Hz, 2H); 6.81 (bs, 2H); 7.22–7.34 (m, 5H). ^{13}C NMR (DMSO-d_6). δ_{ppm}: 13.9 p; 14.1 p; 29.4 p; 48.6 s; 54.0 s; 56.2 s; 60.3 s; 87.9 q; 126.9 t; 128.2 t; 128.6 t; 138.8 q; 159.7 q; 160.3 q; 161.6 q; 171.8 q. IR (KBr) ν (cm^{-1}): 3440 (m); 3331 (m); 2983 (w); 2928 (w); 1734 (m); 1607 (s); 1530 (s); 1454 (m). MS (70 eV) *m*/*z* (%): 285 (63); 192 (68); 184 (100); 120 (21); 106 (11); 91 (78). HR MS: calc for $C_{18}H_{24}N_4O_3S$ 376.1569; found 376.1564.

*4.2. Cyclization attempts of derivatives **3**. Synthesis of methylene bis-pyrimidines (**4**)*

*4.2.1. 1,9-Dimethyl-4,6-bis((triphenyl-λ^5-phosphanylidene) amino)-5,9-dihydro-2H-pyrano[2,3-d:6,5-d']dipyrimidine-2,8 (1H)dione (**4a**)*

CCl_4 (0.3 mL), NEt_3 (2 mmol) and PPh_3 (2 mmol) were added in such order to a suspension of **3a** (1 mmol) in 20 ml of CH_3CN. The resulting mixture was heated to reflux for 19 h and after that filtered hot. The product obtained is a colourless solid. Yield: 47%. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.39 (s, 6H,

2 N-CH_3); 3.88 (s, 2H, C(5)H_2); 7.44–7.52 (m, 12H, H_o of six Ph); 7.52–7.60 (m, 6H, H_m of six Ph); 7.90–7.95 (m, 12H, H_p of six Ph). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 20.1 s (C5); 28.7 p (N(1,9)-CH_3); 89.9 q (d, 25.5 Hz, C4a, C5a); 128.4 q (d, 99.8 Hz, C_i of six Ph); 128.5 t (d, 11.7 Hz, C_o of six Ph); 132.1 t (C_p of six Ph); 133.4 t (d, 2.9 Hz, C_m of six Ph); 151.9 q (C2, C8); 155.1 q (C9a, C10a); 169.9 q (d, 6.6 Hz, C4, C6). MS (70 eV) *m/z* (%): 796 (M^+, 3); 534 (10); 477 (6); 400 (11); 301 (21); 277 (100); 262 (42); 199 (7); 152 (20); 108 (22); 77 (29). HR MS: calc for $C_{47}H_{38}N_6O_3P_2$ 796.2481; found 796.2493.

*4.2.2. 5,5′-Methylenebis[2-methoxy-3-methyl-6-(trimethylsilylamino)pyrimidin-4(3H)-one] (**4b**)*

Hexamethyldisilazane (HDMS) (4.5 mmol) and anhydrous $(NH_4)_2SO_4$ (0.15 mmol) were added to a suspension of **3b** (1 mmol) in 1 ml of THF. The resulting mixture is irradiated with MW and continuous stirring during 25 min at 150 °C (max. power 300 W). Then, 10 ml of MeOH is poured over the reaction mixture and the solid (**3b**) is filtered. The solution is dried and the product is isolated by column chromatography (silicagel, Hexane/AcOEt, 7:3). Yield: 43%. M.p. 228 – 9 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 0.27 (s, 18H, 2 Si(CH_3)$_3$); 3.32 (s, 6H, 2 N-CH_3); 3.51 (s, 2H, CH_2); 3.91 (s, 6H, OCH_3); 7.19 (bs, 2H, two 6-NHSi). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 0.4 p (Si-CH_3); 19.2 s (CH_2); 27.7 p (N-CH_3); 55.15 p (OCH_3); 93.9 q (C5); 154.1 q (C2); 162.1 q (C6); 164.3 q (C4). MS (70 eV) *m/z* (%): 466 (M^+, 9); 451 (8); 394 (11); 305 (8); 240 (11); 168 (10); 73 (100). HR MS: calc for $C_{19}H_{34}N_6O_4Si_2$ 466.2180; found 466.2179.

*4.2.3. 5,5′-Methylenebis[6-amino-3-methyl-2-(methylthio)pyrimidin-4(3H)-one] (**4c**)*

From 0.390 g of **3c** (1 mmol), 1.0 ml de hexamethyldisilazane (HMDS) (4.5 mmol) and 0.02 g of $(NH_4)_2SO_4$ (0.15 mmol) in 1 ml of THF. The mixture is irradiated with microwaves during 25 min. at 150 °C (power max. 300 W). Then, 10 ml of MeOH is added and stirred during 10 h. The product is filtered and the solid is washed with MeOH. Yield: 68%. M.p. > 300 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.51 (s, 6H, 2 SCH_3); 3.36 (s, 6H, 2 N-CH_3); 3.36 (s, 2H, CH_2); 6.72 (bs, 4H, two 6-NH_2). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 13.5 p (S-CH_3); 18.1 s (CH_2); 29.3 p (N—CH_3); 91.2 q (C5); 158.6 q (C2);159.0 q (C6); 162.7 q (C4). IR (KBr) ν (cm^{-1}): 3328 (m, b); 3176 (m, b); 2924 (w, b); 1722 (w); 1633 (s, b); 1511 (s); 1412 (s, b); 1101 (s, b). MS (70 eV) *m/z* (%): 354 (M^+, 50); 339 (13); 290 (13); 249 (28); 184 (28); 88 (100). HR MS: calc for $C_{13}H_{18}N_6O_2S_2$ 354.0933; found 354.0935.

*4.3. Preparation of intermediates (6-aminopyrimidin-5-yl)methyl(substituted)amino acyl halides (**5, 6 & 7**)*

Anhydrous triethylamine (0.14 ml) was added to a solution of 6-amino-5-((substituted-amino)methyl)pyrimidin-4(3H)-one **2** (1 mmol) in 10 ml of THF anhydrous and the mixture was cooled down to 0 °C. Then the corresponding haloacyl halide was added drop-wise with continuous stirring for 5 min. The white solid in suspension (NEt_3·HCl) was removed by filtration and washed with cold THF. The solvent was removed under reduced pressure and the solid residue was recrystallized from a mixture ethanol – hexane (1:1), to give yields > 99% for derivatives **5** and **6**.

*4.3.1. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-2-chloro-N-phenylacetamide (**5a**)*

From 0.260 g of *6-amino-2-methoxy-3-methyl-5-((phenylamino)methyl)pyrimidin-4(3H)-one* (**2a**) and 0.08 ml of chloroacetyl chloride. The white solid filtered contains a small amount of the product, so the solid is digested in hot THF and the solid in suspension filtered hot. M.p. 214 – 6 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.15 (s, 3H); 3.83 (s, 2H); 3.93 (s, 3H); 4.85 (s, 2H); 5.40–6.25 (bs, 2H); 7.15–7.17 (m, 2H); 7.36–7.39 (m, 3H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.5 p; 42.0 s; 44.6 s; 55.2 p; 87.3 q; 127.8 t; 128.9 t; 129.7 t; 140.4 q; 156.0 q; 160.1 q; 163.2 q; 167.7 q. IR (KBr) ν (cm^{-1}): 3391 (m); 3322 (m); 3211 (m); 2950 (w); 1658 (s); 1630 (s); 1534 (s); 1408 (m). MS (70 eV) *m/z* (%): 336 (M^+, 1); 259 (12); 168 (100); 111 (18); 77 (4). HR MS: calc for $C_{15}H_{17}N_4O_3Cl$ 336.0989; found 336.0992.

*4.3.2. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-2-chloro-N-phenylpropanamide (**5b**)*

From 0.260 g of **2a** and 0.100 ml of 2-chloropropionyl chloride. M.p. 178 – 9 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.56 (d, 6.6 Hz, 3H); 3.14 (s, 3H); 3.94 (s, 3H); 4.24 (q, 6.6 Hz, 1H); 4.80 (d, 14.5 Hz, 1H); 4.91 (d, 14.5 Hz, 1H); 5.40–6.20 (bs, 2H); 7.17 (bs, 2H); 7.36–4.40 (m, 3H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 21.4 p; 27.5 p; 44.3 s; 50.4 t; 55.2 p; 87.1 q; 127.9 t; 128.7 t; 129.6 t; 140.4 q; 156.0q; 160.1 q; 163.1 q; 171.0 q. IR (KBr) ν (cm^{-1}): 3385 (m, b); 3327 (m); 3214 (m); 2941 (w); 1652 (s, b); 1597 (m); 1510 (s); 1411(s); 1225 (m). MS (70 eV) *m/z* (%): 350 (M^+, 1%); 259 (14); 168 (100); 111 (14). HR MS: calc for $C_{16}H_{19}N_4O_3Cl$ 350.1146; found 350.1148.

*4.3.3. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-2-chloro-N,2-diphenylacetamide (**5c**)*

From 0.260 g of **2a** and 0.161 ml of 2-chloro-2-phenylacetyl chloride. M.p. 156 – 8 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.12 (s, 3H); 3.92 (s, 3H); 4.79 (d, 14.6 Hz, 1H); 4.90 (d, 14.6 Hz, 1H); 5.28 (s, 1H); 5.40–6.25 (bs, 2H); 6.83 (bs, 1H); 7.26–7.31 (m, 7H); 7.37–7.45 (m, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.5 p; 44.7 s; 55.1 p; 57.1 t; 87.0 q; 127.9 t; 128.1 t; 128.6 t; 129.0 t; 129.5 t; 129.6 t; 136.3 q; 140.3 q; 156.0 q; 160.1 q; 163.1 q; 169.1 q. IR (KBr) ν (cm^{-1}): 3445 (m); 3325 (m); 3222 (m); 3062 (w); 3031 (w); 2964 (w); 1655 (s); 1629 (s, b); 1595 (m); 1551 (s); 1494 (m); 1485 (m). MS (70 eV) *m/z* (%): 412 (M^+, 0.4); 259 (15); 168 (100); 111 (11); 89 (2); 72 (3). HR MS: calc for $C_{21}H_{21}N_4O_3Cl$ 412.1302; found 412.1309.

*4.3.4. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzyl-2-chloroacetamide (**5d**)*

From 0.274 g of *6-amino-5-((benzylamino)methyl)-2-methoxy-3-methylpyrimidin-4(3H)-one* (**2b**) and 0.080 ml of chloroacetyl chloride. M.p. 134 – 6 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.29 (s, 3H); 3.94 (s, 3H); 4.05 (s, 2H); 4.53 (s, 2H); 4.81 (s, 2H); 5.55–6.36 (bs, 2H); 7.23–7.29 (m, 3H); 7.35 (pt, 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.6 p; 41.6 s; 42.0 s; 51.6 s; 55.3 p; 88.5 q; 126.2 t; 127.6 t; 128.9 t; 136.5 q; 156.0 q; 160.8 q; 164.3 q; 168.6 q. IR (KBr) ν (cm^{-1}): 3329 (m, b);

3189 (m); 2949 (w); 1639 (s, b); 1588 (m); 1556 (s, b); 1482 (m). MS (70 eV) *m/z* (%): 350 (M^+, 2); 273 (15); 259 (31); 183 (24); 168 (100); 111 (23); 91 (41). HR MS: calc for $C_{16}H_{19}N_4O_3Cl$ 350.1146; found 350.1148.

*4.3.5. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzyl-2-chloropropanamide (**5e**)*

From 0.274 g of **2b** and 0.100 ml of 2-chloropropionyl chloride. M.p. 117 – 20 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.58 (d, 6.6 Hz, 3H); 3.29 (s, 3H); 3.94 (s, 3H); 4.43 (d, 14.6 Hz, 1H); 4.51 (q, 6.6 Hz, 1H); 4.65 (d, 14.6 Hz, 1H); 4.81 (d, 17.3 Hz, 1H); 4.88 (d, 17.3 Hz, 1H); 5.57–6.30 (bs, 2H); 7.21–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 21.1 p; 27.6 p; 41.6 s; 49.6 t; 51.1 s; 55.3 p; 88.3 q; 126.0 t; 127.5 t; 128.9 t; 136.9 q; 156.0 q; 160.9 q; 164.3 q; 171.5 q. IR (KBr) ν (cm^{-1}): 3329 (m, b); 3183 (m); 2958 (w); 1640 (s, b); 1586 (m); 1557 (s); 1541 (s); 1452 (m). MS (70 eV) *m/z* (%): 364 (M^+, 3); 273 (62); 183 (21); 168 (100); 154 (4); 111 (14); 91 (16); 57 (8). HR MS: calc for $C_{17}H_{21}N_4O_3Cl$ 364.1302; found 364.1294.

*4.3.6. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzyl-2-chloro-2-phenylacetamide (**5f**)*

From 0.274 g of **2b** and 0.161 ml of 2-chloro-2-phenylacetyl chloride. M.p. 147 – 8 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.26 (s, 3H); 3.93 (s, 3H); 4.55 (d, 14.7 Hz, 1H); 4.59 (d, 14.7 Hz, 1H); 4.76 (d, 17.4 Hz, 1H); 4.85 (d, 17.4 Hz, 1H); 5.53 (s, 1H); 5.60–6.40 (bs, 2H); 7.21–7.37 (m, 10H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.6 p; 42.4 s; 51.4 s; 55.3 p; 57.2 t; 88.2 q; 126.0 t; 127.6 t; 128.2 t; 128.8 t; 129.0 t; 129.1 t; 135.9 q; 136.7 q; 156.0 q; 160.8 q; 164.3 q; 169.8 q. IR (KBr) ν (cm^{-1}): 3385 (m, b); 3213 (m); 3030 (w); 2959 (w); 1649 (s, b); 1590 (m); 1542 (s, b); 1488 (m); 1457 (m); 1216 (m). MS (70 eV) *m/z* (%): 426 (M^+, 1); 335 (13); 272 (31); 168 (100); 111 (12); 91 (24). HR MS: calc for $C_{22}H_{23}N_4O_3Cl$ 426.1459; found 426.1456.

*4.3.7. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzyl-2-chloro-2,2-diphenylacetamide (**5g**)*

From 0.274 g of **2b** and 0.273 ml of 2-chloro-2,2-diphenylacetyl chloride. M.p. 131 – 5 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.23 (s, 3H); 3.94 (s, 3H); 4.45 (s, 2H); 4.60 (s, 2H); 5.60-6.30 (bs, 2H); 7.22–7.34 (m, 15H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.6 p; 41.9 s; 53.2 s; 55.2 p; 75.5 q; 88.6 q; 127.2 t; 127.6 t; 128.0 t; 128.2 t; 128.4 t; 128.6 t; 129.0 t; 129.9 t; 130.6 t; 136.8 q; 141.4 q; 155.9 q; 160.9 q; 164.1 q; 171.5 q. IR (KBr) ν (cm^{-1}): 3386 (m, b); 3312 (m); 3203 (m, b); 3064 (w); 3032 (w); 2954 (w, b); 1719 (m); 1655 (s); 1621 (s, b); 1583 (m); 1540 (f); 1485 (m); 1447 (m); 1411 (m). MS (70 eV) *m/z* (%): 466 (M-HCl, 10); 453 (8); 347 (56); 333 (40); 272 (27); 194 (100); 165 (76); 91 (60).

*4.3.8. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzyl-2-bromobutanamide (**5h**)*

From 0.274 g of **2b** and 0.135 ml of 2-bromobutyryl bromide. M.p. 141 – 3 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 0.83 (t, 7.3 Hz, 3H); 1.90–2.00 (m, 1H); 2.05–2.16 (m, 1H); 3.29 (s, 3H); 3.94 (s, 3H); 4.21 (t, 7.2 Hz, 1H); 4.46 (d, 14.5 Hz, 1H); 4.68–4.73 (m, 2H); 4.89 (d, 17.4 Hz, 1H); 5.60–6.31 (bs, 2H); 7.20–7.28 (m, 3H); 7.34 (pt, 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 12.1 p; 27.6 p; 28.4 s; 41.7 s; 45.4 t; 51.3 s; 55.3 p; 88.1 q; 126.0 t; 127.4 t; 128.8 t; 137.1 q; 156.0 q; 160.9 q; 164.3 q; 171.3 q. IR (KBr) ν (cm^{-1}): 3336 (s, b); 3179 (s); 2959 (m); 1640 (s, b); 1581 (s); 1557 (s, b); 1483 (s); 1450 (s, b); 1416 (s); 1213 (m). MS (70 eV) *m/z* (%): 422/424 (M/M + 2, 1/1); 348 (3); 331 (10); 273 (25); 210 (17); 183 (13); 168 (100); 111 (8); 91 (11). HR MS: calc for $C_{18}H_{23}N_4O_3Br$ 422.0954; found 422.0958.

*4.3.9. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzyl-2-bromohexanamide (**5i**)*

From 0.274 g of **2b** and 0.167 ml of 2-bromohexanoyl bromide. M.p. 132 – 3 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 0.81 (t, 7.0 Hz, 3H); 1.08–1.25 (m, 4H); 1.89–1.97 (m, 1H); 2.02–2.11 (m, 1H); 3.29 (s, 3H); 3.94 (s, 3H); 4.27 (t, 7.2 Hz, 1H); 4.46 (d, 14.5 Hz, 1H); 4.68–4.73 (m, 2H); 4.89 (d, 17.1 Hz,1H); 5.62–6.42 (sa, 2H); 7.21–7.28 (m, 3H); 7.34 (pt, 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 13.7 p; 22.0 s; 27.6 p; 29.4 s; 34.6 s; 41.8 s; 43.9 t; 51.3 s; 55.3 p; 88.0 q; 126.0 t; 127.4 t; 128.8 t; 137.2 q; 156.0 q; 160.9 q; 164.3 q; 171.5 q. IR (KBr) ν (cm^{-1}): 3409 (m); 3334 (m); 3218 (m); 2955 (m); 2870 (m); 1657 (s, b); 1624 (s, b); 1592 (s); 1543 (s, b); 1484 (s); 1215 (m). MS (70 eV) *m/z* (%): 450/452 (M/M + 2, 1/1); 371 (3); 361 (10); 359 (10); 273 (28); 238 (18); 183 (13); 168 (100); 111 (11); 91 (14). HR MS: calc for $C_{20}H_{27}N_4O_3Br$ 450.1267; found 450.1265.

Crystal data for **5i** were deposited at CCDC with reference CCDC 1,037,317: Chemical formula $C_{20}H_{27}BrN_4O_3$, M_r 450.13, triclinic, *P*-1, 120 K, cell dimensions *a, b, c* (Å) 8.6720 (8), 8.9471 (6), 13.9607 (17); *α, β, γ* (°) 78.450 (8), 89.372 (7), 74.219 (8). *V* (Å^3) 1020.18 (17), *Z* = 2, *F*(000) = 468, D_x (Mg m^{-3}) = 1.469, Mo *K*α, μ (mm^{-1}) = 2.043, Crystal size (mm) = 0.37 × 0.28 × 0.27. Data collection: KappaCCD Diffractometer, Monochromator graphite, CCD rotation images, thick slices φ & θ scans, absorption correction *SADABS* 2.10, *T*min, *T*max 0.5185, 0.6084 No. of measured, independent and observed [$I > 2\sigma(I)$] reflections 35,442, 4676, 3855, *R*int = 0.044, *θ* values (°): *θ*max = 27.5, *θ*min = 2.92; Range $h = -11 \rightarrow 11$, $k = -11 \rightarrow 11$, $l = -18 \rightarrow 18$, Refinement on $F2$:$R[F2 > 2\sigma(F2)] = 0.036$, $wR(F2) = 0.072$, $S = 1.06$. No. of reflections 4676, No. of parameters 256, No. of restraints 0. Weighting scheme: $w = 1/\sigma^2(F_o^2) + (0.0263P)^2 + 1.0085P$ where $P = (F_o^2 + 2F_c^2)/3$. $(\Delta/\sigma) < 0.001$, $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3}) 0.39, −0.44.

*4.3.10. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzyl-2-bromo-2-methylpropanamide (**5j**)*

From 0.274 g of **2b** and 0.126 ml of 2-bromoisobutyryl bromide. M.p. 159 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.94 (s, 6H); 3.25 (s, 3H); 3.92 (s, 3H); 4.41 (s, 2H); 5.23 (s, 2H); 5.53–6.33 (bs, 2H); 7.21–7.27 (m, 3H); 7.33 (pt, 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.6 p; 33.1 p; 42.4 s; 52.9 s; 55.2 p; 57.1 q; 89.1 q; 126.5 t; 126.9 t; 128.5 t; 137.2 q; 155.8 q; 160.9 q; 164.3 q; 172.3 q. IR (KBr) ν (cm^{-1}): 3353 (m); 3319 (m); 3182 (m); 3007 (w); 2933 (w); 1643 (s, b); 1616 (s); 1552 (s, b); 1452 (m); 1416 (m); 1219 (m); 1169 (m). MS (70 eV) *m/z* (%): 422/424 (M/M + 2, 1/1); 333 (14); 331 (14); 210 (17); 168 (100); 111 (10); 91 (11). HR MS: calc for $C_{18}H_{23}N_4O_3Br$ 422.0954; found 422.0950.

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*4.3.11. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-2-chloro-N-cyclohexylacetamide (**5k**)*

From 0.266 g of *6-amino-5-((cyclohexylamino)methyl)-2-methoxy-3-methylpyrimidin-4(3H)-one* (**2c**) and 0.08 ml of chloroacetyl chloride. M.p. 193 – 5 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.18–1.32 (m, 3H); 1.60–1.67 (m, 3H); 1.75–1.85 (m, 2H); 1.92–2.01 (m, 2H); 3.34 (s, 3H); 3.55 (tt, 3.5 Hz and 12.0 Hz, 1H); 3.93 (s, 3H); 4.18 (s, 2H); 4.58 (s, 2H); 5.55–6.35 (bs, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 24.9 s; 26.3 s; 27.7 p; 30.9 s; 42.3 s; 55.1 p; 59.6 t; 89.1 q; 155.7 q; 160.2 q; 163.2 q; 168.2 q. IR (KBr) ν (cm^{-1}): 3369 (m, b); 3201 (m); 2936 (m); 2860 (w); 1643 (s, b); 1595 (m); 1538 (s, b); 1488 (m); 1453 (m); 1222 (m). MS (70 eV) *m*/*z* (%): 342 (M^+, 2); 265 (100); 259 (35); 183 (31); 168 (54); 111 (12). HR MS: calc for $C_{15}H_{23}N_4O_3Cl$ 342.1459; found 342.1457.

*4.3.12. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-2-chloro-N-cyclohexylpropanamide (**5l**)*

From 0.266 g of **2c** and 0.100 ml of 2-chloropropyl chloride. M.p. 160 – 1 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.17–1.34 (m, 3H); 1.55–1.63 (m, 2H); 1.69 (d, 6.4 Hz, 3H); 1.74–1.84 (m, 3H); 1.89–1.98 (m, 2H); 3.33 (s, 3H); 3.68–3.74 (m, 1H); 3.93 (s, 3H); 4.60 (s, 2H); 4.70 (q, 6.4 Hz, 1H); 5.55–6.35 (bs, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 21.7 p; 25.0 s; 26.4 s; 27.7 p; 31.6 s; 37.0 s; 50.6 t; 55.1 p; 59.0 t; 89.2 q; 155.6 q; 160.2 q; 163.25 q; 171.05 q. IR (KBr) ν (cm^{-1}): 3380 (s, b); 3172 (m, b); 2934 (m); 2858 (m); 1635 (s, b); 1591 (s); 1538 (s, b); 1451 (s); 1222 (m). MS (70 eV) *m*/*z* (%): 356 (M^+, 1); 273 (29); 265 (100); 259 (35); 183 (27); 168 (57); 111 (10). HR MS: calc for $C_{16}H_{25}N_4O_3Cl$ 356.1615; found 356.1618.

*4.3.13. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-2-chloro-N-cyclohexyl-2,2-diphenylacetamide (**5m**)*

From 0.266 g of **2c** and 0.273 ml of 2-chloro-2,2-diphenyl chloride. The product is isolated by column chromatography (DCM/MeOH, 95:5). M.p. 178 – 80 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 0.64 (qt, 3.3 and 13.0 Hz, 2H); 1.03 (qt, 3.9 and 13.2 Hz, 1H); 1.27–1.39 (m, 3H); 1.48 (pd, 13.0 Hz, 2H); 1,6-1.7 (bs, 1.3 Hz); 1.73 (qd, 3.3 and 11.8 HZ, 2H); 3.31 (s, 3H); 3.80 (tt, 2.7 and 11.5 Hz, 1H); 3.95 (s, 3H); 4.69 (s, 2H); 7.26–7.37 (m, 10H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 25.0 s; 26.2 s; 27.7 p; 30.0 s; 37.3 s; 55.1 p; 59.4 t; 76.9 q; 89.7 q; 127.8 t; 128.1 t; 128.5 t; 141.5 q; 155.6 q; 160.0 q; 163.3 q; 171.5 q. IR (KBr) ν (cm^{-1}): 3418 (m); 3191 (m); 3077 (w); 3008 (w); 2932 (m); 2853 (m); 1650 (s, b); 1619 (s); 1587 (m); 1538 (s); 1488 (m); 1448 (m); 1208 (m). MS (70 eV) *m*/*z* (%): 458 (M-HCl, 6); 444 (14); 333 (61); 304 (20); 194 (100); 166 (48); 55 (15). HR MS: calc for $C_{27}H_{30}N_4O_3$ (M-HCl) 458.2318; found 458.2308.

*4.3.14. N-{[4-Amino-1-methyl-2-methylthio-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-2-chloro-N-phenylacetamide (**5n**)*

From 0.276 g of *6-amino-3-methyl-2-methylthio-5-((phenylamino)methyl)pyrimidin-4(3H)-one* (**2d**) and 0.08 ml of chloroacetyl chloride. The white solid filtered contains a small amount of the product, so the solid is digested in hot THF and the solid in suspension filtered hot. M.p. 192 – 4 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.51 (s, 3H); 3.26 (s, 3H); 3.83 (s, 2H); 4.87 (s, 2H); 5.43–6.20 (bs, 2H); 7.13–7.20 (m, 2H); 7.35–7.42 (m, 3H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.7 p; 30.0 p; 41.9 s; 44.5 s; 88.95 q; 127.7 t; 128.9 t; 129.75 t; 140.4 q; 159.3 q; 161.8 q; 162.5 q; 167.8 q. IR (KBr) ν (cm^{-1}): 3424 (m); 3324 (m); 3237 (w); 2942 (w); 1655 (s); 1616 (s); 1576 (m); 1530 (s); 1493 (m); 1454 (m). MS (70 eV) *m*/*z* (%): 352 (M^+, 1); 275 (16); 184 (100); 93 (5); 88 (9); 77 (5). HR MS: calc for $C_{15}H_{17}N_4O_2SCl$ 352.0761; found 352.0760.

*4.3.15. N-{[4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-2-chloro-N-phenylpropanamide (**5o**)*

From 0.276 g of **2d** and 0.100 ml of 2-chloropropionyl chloride. M.p. 162 – 4 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.57 (d, 6.6 Hz, 3H); 2.51 (s, 3H); 3.25 (s, 3H); 4.24 (q, 6.6 Hz, 1H); 4.82 (d, 14.7 Hz, 1H); 4.92 (d, 14.7 Hz, 1H); 5.45–6.25 (bs, 2H); 7.18 (bs, 2H); 7.35–7.42 (m, 3H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 21.4 p; 29.9 p; 44.2 s; 50.3 t; 88.8 q; 127.9 t; 128.8 t; 129.6 t; 140.4 q; 159.3 q; 161.7 q; 162.5 q; 171.1 q. IR (KBr) ν (cm^{-1}): 3396 (m); 3327 (m); 3226 (w); 3209 (w); 2932 (w); 1650 (s); 1616 (s); 1571 (m); 1529 (m); 1409 (m). MS (70 eV) *m*/*z* (%): 366 (M^+, 1); 275 (19); 183 (100); 88 (2). HR MS: calc for $C_{16}H_{19}N_4O_2SCl$ 366.0917; found 366.0926.

*4.3.16. N-{[4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-2-chloro-N,2-diphenylpropanamide (**5p**)*

From 0.276 g of **2d** and 0.161 ml of 2-phenyl-2-chloroacetyl chloride. M.p. 156 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.50 (s, 3H); 3.23 (s, 3H); 4.81 (d, 14.6 Hz, 1H); 4.91 (d, 14.6 Hz, 1H); 5.28 (s, 1H); 5.50–6.30 (bs, 2H); 6.83 (bs, 1H); 7.25–7.35 (m, 7H); 7.35–7.45 (m, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 29.9 p; 44.65 s; 57.1 t; 88.7 q; 127. 9 t; 128.1 t; 128.6 t; 128.9 t; 129.6 t; 129.7 t; 136.2 q; 140.3 q; 159.3 q; 161.8 q; 162.45 q; 169.2 q. IR (KBr) ν (cm^{-1}): 3324 (m); 3231 (w); 2927 (w); 1662 (m); 1613 (s); 1575 (m); 1529 (m). MS (70 eV) *m*/*z* (%): 428 (M^+, 0.4); 275 (21); 258 (2); 184 (100); 125 (4); 88 (4). HR MS: calc for $C_{21}H_{21}N_4O_2SCl$ 428.1074; found 428.1078.

*4.3.17. N-{[4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-N-benzyl-2-chloroacetamide (**5q**)*

From 0.290 g of *6-amino-5-((benzylamino)methyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one* (**2e**) and 0.080 ml of chloroacetyl chloride. M.p. 157 – 8 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.51 (s, 3H); 3.39 (s, 3H); 4.05 (s, 2H); 4.54 (s, 2H); 4.81 (s, 2H); 5.44–6.48 (bs, 2H); 7.21–7.30 (m, 3H); 7.32–7.38 (m, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.7 p; 30.0 p; 41.5 s; 41.9 s; 51.7 s; 90.2 q; 126.2 t; 127.6 t; 128.9 t; 136.4 q; 159.9 q; 161.9 q; 163.6 q; 168.6 q. IR (KBr) ν (cm^{-1}): 3345 (m, b); 3195 (m); 2933 (w); 1634 (s); 1610 (s); 1572 (m); 1533 (s); 1511 (m), 1453 (m); 1415 (m). MS (70 eV) *m*/*z* (%): 366 (M^+, 2); 289 (15); 275 (34); 199 (26); 184 (100); 91 (34); 88 (17). HR MS: calc for $C_{16}H_{19}N_4O_2SCl$ 366.0917; found 366.0922.

*4.3.18. N-{[4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-N-benzyl-2-chloropropanamide (**5r**)*

From 0.290 g of **2e** and 0.100 ml of 2-chloropropionyl chloride. M.p. 176 – 9 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.59 (d, 6.6 Hz, 3H); 2.51 (s, 3H); 3.40 (s, 3H); 4.45 (d, 14.5 Hz, 1H);

4.52 (q, 6.6 Hz, 1H); 4,65 (d, 14.5 Hz, 1H); 4.82 (d, 17.2 Hz, 1H); 4.88 (d, 17.2 Hz, 1H); 5.64–6.38 (bs, 2H); 7.20–7.24 (m, 2H); 7.25–7.30 (m, 1H); 7.32–7.38 (m, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.7 p; 21.1 p; 30.1 p; 41.6 s; 49.6 t; 51.2 s; 90.0 q; 126.0 t; 127.5 t; 128.9 t; 136.8 q; 160.0 q; 161.8 q; 163.6 q; 171.6 q. IR (KBr) ν (cm^{-1}): 3341 (m, b); 3195 (m); 2934 (w); 1635 (s); 1614 (s); 1534 (m); 1511 (m); 1450 (m); 1415 (m). MS (70 eV) *m/z* (%): 380 (M^+, 2); 289 (56); 199 (24); 183 (100); 91 (25); 88 (12). HR MS: calc for $C_{17}H_{21}N_4O_2SCl$ 380.1074; found 380.1073.

*4.3.19. N-{[4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-N-benzyl-2-chloro-2-phenylacetamide (**5s**)*

From 0.290 g of **2e** and 0.161 ml of 2-chloro-2-phenylacetyl chloride. M.p. 153 – 6 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.50 (s, 3H); 3.37 (s, 3H); 4.58 (s, 2H); 4.77 (d, 17.3 Hz, 1H); 4.85 (d, 17.3 Hz, 1H); 5.54 (s, 1H); 5.58–6.53 (bs, 2H); 7.20–7.39 (m, 10H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.7 p; 30.0 p; 42.3 s; 51.5 s; 57.15 t; 89.9 q; 126.0 t; 127.6; 128.2 t; 128.8 t; 129.0 t; 129.1 t; 135.9 q; 136.6 q; 160.0 q; 161.9 q; 163.6 q; 169.9 q. IR (KBr) ν (cm^{-1}): 3354 (m); 3317 (m); 3179 (m); 2932 (w); 1645 (s); 1614 (s); 1534 (m); 1515 (m); 1454 (m); 1419 (m). MS (70 eV) *m/z* (%): 442 (M^+, 0.3); 351 (M^+ –91, 12); 288 (67); 273 (16); 258 (15); 197 (43); 184 (100); 91 (45). HR MS: calc for $C_{22}H_{23}N_4O_2SCl$ 442.1230; found 442.1226.

*4.3.20. N-{[4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-N-benzyl-2-chloro-2,2-diphenylacetamide (**5t**)*

From 0.290 g of **2e** and 0.273 ml of 2-chloro-2,2-diphenylacetyl chloride. M.p. 144 – 5 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.51 (s, 3H); 3.33 (s, 3H); 4.46 (s, 2H); 4.61 (s, 2H); 5.50–6.50 (bs, 2H) 7.15–7.40 (m, 15H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.7 p; 30.1 p; 42.0 s; 53.4 s; 60.1 q; 90.3 q; 127.6 t; 127.7 t; 128.05 t; 128.6 t; 128.6 t; 128.7 t; 128.9 t; 129.8 t; 130.5 t; 134.9 q; 136.7 q; 141.3 q; 160.0 q; 161.6 q; 163.3, q; 171.6 q. IR (KBr) ν (cm^{-1}): 3418 (m); 3325 (m); 3061 (w); 3025 (w); 2941 (w); 1612 (s, b); 1523 (s); 1446 (m); 1411 (m). MS (70 eV) *m/z* (%): 482 (M^+-HCl, 8); 363 (74), 334 (47); 194 (62); 165 (100); 91 (40); 88 (16). HR MS: calc for $C_{28}H_{26}N_4O_2S$ (M-HCl) 482.1776; found 482.1782.

*4.3.21. N-{[4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-N-benzyl-2-bromobutanamide (**5u**)*

From 0.290 g of **2e** and 0.135 ml of 2-bromobutyryl bromide. M.p. 124 – 6 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 0.84 (t, 7.3 Hz, 3H); 1.91–2.02 (m, 1H); 2.06–2.16 (m, 1H); 2.51 (s, 3H); 3.39 (s, 3H); 4.22 (t, 7.3 Hz, 1H); 4.48 (d; 14.7 Hz, 1H); 4.66–4.76 (m, 2H); 4.88 (d, 17.3 Hz, 1H); 5.62–6.42 (bs, 2H); 7.20–7.29 (m, 3H); 7.31–7.37 (m, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 12.1 p; 14.7 p; 28.4 s; 30.05 p; 41.6 s; 45.3 t; 51.35 s; 89.7 q; 126.0 t; 127.5 t; 128.8 t; 137.0 q; 160.0 q; 161.8 q; 163.6 q; 171.4 q. IR (KBr) ν (cm^{-1}): 3349 (m, b); 3184 (m); 2973 (w); 2932 (w); 2873 (w); 1625 (s, b); 1611 (s, b); 1568 (m); 1531 (s, b); 1448 (m); 1413 (m). MS (70 eV) *m/z* (%): 438/440 (M^+ 2/M + 2, 1:1); 349 (10); 347 (10); 289 (24); 199 (17); 183 (100); 91 (8); 88 (3). HR MS: calc for $C_{18}H_{23}N_4O_2SBr$ 438.0725; found 438.0735.

*4.3.22. N-{[4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-N-benzyl-2-bromohexanamide (**5v**)*

From 0.290 g of **2e** and 0.167 ml of 2-bromohexanoyl bromide. M.p. 105 – 8 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 0.81 (t, 7.0 Hz, 3H); 1.08–1.25 (m, 4H); 1.88–1.98 (m, 1H); 2.02–2.12 (m, 1H); 2.51 (s, 3H); 3.40 (s, 3H); 4.28 (t, 7.2 Hz, 1H); 4.48 (d, 14.5 Hz, 1H); 4.69–4.74 (m, 2H); 4.89 (d, 17.3 Hz, 1H); 5.54–6.58 (bs, 2H); 7.19–7.29 (m, 3H); 7.31–7.37 (m, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 13.7 p; 14.7 p; 22.0 s; 29.4 s; 30.1 p; 34.6 s; 41.7 s; 43.8 t; 51.35 s; 89.7 q; 126.0 t; 127.5 t; 128.8 t; 137.05 q; 160.0 q; 161.8 q; 163.6 q; 171.6 q. IR (KBr) ν (cm^{-1}): 3357 (m, b); 3317 (m, b); 3192 (m); 2957 (m); 2931 (m); 1636 (s, b); 1596 (s, b); 1571 (m); 1533 (s); 1517 (s); 1453 (m); 1417 (m). MS (70 eV) *m/z* (%): 466/468 (M^+ 2/M + 2, 0.1:0.1) 375 (3); 289 (7); 204 (61); 184 (34); 91 (100). HR MS: calc for $C_{20}H_{27}N_4O_2SBr$ 466.1038; found 466.1050.

*4.3.23. N-{[4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-2-chloro-N-cyclohexylacetamide (**5w**)*

From 0.282 g of *6-amino-5-((cyclohexylamino)methyl)-3-methyl-2-methylthiopyrimidin-4(3H)-one* (**2f**) and 0.08 ml de chloroacetyl chloride. M.P. 148 – 51 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.21–1.30 (m, 3H); 1.59–1.67 (m, 3H); 1.81–1.84 (m, 2H); 1.90–2.00 (m, 2H); 2.49 (s, 3H); 3.44 (s, 3H); 3.55 (tt, 3.3 Hz & 11.8 Hz, 1H); 4.18 (s, 2H); 4.60 (s, 2H); 4.90–6.90 (bs, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 24.9 s; 26.3 s; 30.2 p; 30.9 s; 36.5 s; 42.2 s; 59.6 t; 90.8 q; 159.4 q; 161.2 q; 162.6 q; 168.3 q. IR (KBr) ν (cm^{-1}): 3380 (s); 3200 (m); 2933 (m); 2858 (m); 1640 (s); 1610 (s, b); 1569 (s); 1524 (s); 1452 (s); 1409 (s); 1102 (m). MS (70 eV) *m/z* (%): 358 (M^+, 2); 281 (100); 274 (38); 199 (43); 183 (61); 88 (12). HR MS: calc for $C_{15}H_{23}N_4O_2SCl$ 358.1230; found 358.1225.

*4.3.24. N-{[4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-2-chloro-N-cyclohexylpropanamide (**5x**)*

From 0.282 g of **2f** and 0.100 ml of 2-chloropropionyl chloride. M.p. 143 – 6 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.18–1.34 (m, 3H); 1.56–1.68 (m, 2H); 1.69 (d, 6.4 Hz, 3H); 1.74–1.84 (m, 3H); 1.89–1.98 (m, 2H); 2.49 (s, 3H); 3.44 (s, 3H); 3.72 (tt, 3.3 Hz and 12.0 Hz, 1H); 4.61 (s, 2H); 4.70 (q, 6.4 Hz,1H); 5.00–7.00 (bs, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 21.7 p; 25.0 s; 26.3 s; 26.4 s; 30.2 p; 30.7 s; 31.6 s; 36.7 s; 50.5 t; 59.0 t; 91.0 q; 159.4 q; 161.1 q; 162.65 q; 171.1 q. IR (KBr) ν (cm^{-1}): 3389 (m); 3189 (m, b); 2932 (m); 2857 (m); 1635 (s); 1612 (s); 1568 (m); 1523 (s); 1452 (m); 1423 (m). MS (70 eV) *m/z* (%): 372 (M^+, 1); 289 (34); 281 (100); 199 (21); 183 (47); 88 (10). HR MS: calc for $C_{16}H_{25}N_4O_4SCl$ 372.1387; found 372.1390.

*4.3.25. N-((4-amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-2-chloro-N-cyclohexyl-2-phenylacetamide (**5y**)*

From 0.282 g of **2f** and 0.161 ml of 2-chloro-2-phenylacetyl chloride. M.p. 264 – 7 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.09–1.17 (m, 3H); 1.51–1.58 (m, 2H); 1.61–1.68 (m, 1H); 1.74–1.84 (m, 2H); 1.89–1.98 (m, 2H); 2.49 (s, 3H); 3.42 (s, 3H); 3.56-3.66 (m, 1H); 4,60 (d, 15.3 Hz, 1H); 4,65 (d, 15.3 Hz, 1H); 5.00–7.00 (bs, 2H); 5,83 (s, 1H); 7.35–7.42 (m, 3H); 7.45–7.50 (m, 2H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 24.9 s;

26.2, s; 26.4 s; 30.2 p; 44.8 s; 59.1 t; 59.9 t; 90.9 q; 127.6 t; 129.0 t; 129.6 t; 136.6 q; 159.4 q; 161.2 q; 162.6 q; 169.3 q. IR (KBr) ν (cm^{-1}): 3408 (m); 3324 (m); 3148 (m, b); 3052 (m); 2934 (m); 2855 (m); 1719 (m); 1682 (s); 1639 (s); 1613 (s); 1520 (s, b); 1451 (s); 1415 (s); 1423 (m). MS (70 eV) *m/z* (%): 399 (M^+-Cl,2); 282 (100); 266 (10); 261 (7); 131 (9); 115 (23); 97 (5); 83 (12).

*4.3.26. N-Benzyl-2-chloro-N-{[4-(2-chloroacetamido)-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl} acetamide (**6a**)*

From 0.274 g of **2b** and 0.160 ml of chloroacetyl chloride at room temperature. M.p. 140 – 2 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.39 (s, 3H, N—CH_3); 4.06 (s, 3H, O—CH_3); 4.07 (s, 2H, NBn—CO—$C\underline{H_2}$Cl); 4.32 (s, 4H, C5—$C\underline{H_2}$—N and 4-N—CO—$C\underline{H_2}$—Cl); 5.01 (s, 2H, Bn); 7.23–7.27 (m, 2H, two H_o Ph); 7.29–7.34 (m, 1H, H_m Ph); 7.35–7.42 (m, 2H, two H_o Ph); 11.00 (bs, 1H, 4—NHCO). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 28.2 p (N—CH_3); 40.9 s (NBn—CO—$C\underline{H_2}$Cl); 42.9 s (C5—$C\underline{H_2}$—N); 43.8 s (4-N—CO—$C\underline{H_2}$—Cl); 53. 2 s (Bn); 58.2 p (O—CH_3); 101.2 q (C5); 126.4 t (C_o Ph); 127.9 t (C_m Ph); 129.1 t (C_p Ph); 136.0 q (C_i Ph); 153.9 q (C2); 155.9 q (C4); 164.6 q (C6); 165.4 q (4-N—$C\underline{O}$—CH_2—Cl); 169.0 q (NBn—$C\underline{O}$—CH_2Cl). IR (KBr) ν (cm^{-1}): 3231 (w); 3201 (w); 3145 (w); 3021 (w); 2951 (w); 1698 (m); 1649 (s, b); 1613 (s); 1558 (s, b); 1494 (s). MS (70 eV) *m/z* (%): 426 (M^+, 1); 335 (41); 244 (70); 180 (29); 168 (43); 111 (24); 106 (31); 91 (100). HR MS: calc for $C_{18}H_{20}N_4O_4Cl_2$ 426.0862; found 426.0858.

*4.3.27. N-Benzyl-2-chloro-N-{[4-(2-chloroacetamido)-(2-methylthio)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl} acetamide (**6b**)*

From 0.290 g of **2e** and 0.160 ml of chloroacetyl chloride at room temperature. M.p. 134 – 5 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.51 (s, 3H, S—CH_3); 3.40 (s, 3H, N—CH_3); 4.08 (s, 2H, NBn—CO—$C\underline{H_2}$Cl); 4.29 (s, 2H, C5—$C\underline{H_2}$—N) 4.34 (s, 2H, 4-N—CO—$C\underline{H_2}$—Cl); 5.00 (s, 2H, Bn); 7.23–7.27 (m, 2H, two H_o Ph); 7.29–7.34 (m, 1H, H_p Ph); 7.36–7.42 (m, 2H, two H_m Ph); 11.00 (s, 1H, 4-NHCO). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 15.0 p (S—CH_3); 28.2 p (N—CH_3); 40.9 s (NBn—CO—$C\underline{H_2}$Cl); 42.9 s (C5—$C\underline{H_2}$—N); 43.8 s (4-N—CO—$C\underline{H_2}$—Cl); 53.2 s (Bn); 102.6 q (C5); 126.4 t (C_o Ph); 127.9 t (C_m Ph); 129.1 t (C_p Ph); 135.9 q (C_i Ph); 153.1 q (C2); 162.9 q (C4); 164.0 q (C6); 165.1 q (4-N—$C\underline{O}$—CH_2—Cl); 169.0 q (NBn—$C\underline{O}$—CH_2Cl). IR (KBr) ν (cm^{-1}): 3006 (w); 2929 (w); 1724 (m); 1658 (s); 1621 (s, b); 1525 (s); 1494 (m); 1481 (m); 1414 (m); 1395 (m). MS (70 eV) *m/z* (%): 351 (M^+ −91, 20); 261 (22); 184 (22); 91 (100). HR MS: calc for $C_{18}H_{20}N_4O_3SCl_2$ 442.0633; found 442.0637.

*4.3.28. N-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzyl-3-chloropropanamide (**10a**)*

From 0.274 g of **2b** and 0.090 ml of 3-chloropropionyl chloride. M.p. 156 – 7 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.77 (t, 6.7 Hz, 2H, CO—$C\underline{H_2}$—CH_2Cl); 3.28 (s, 3H, N—CH_3); 3.79 (t, 6.7 Hz, 2H, CO—CH_2—$C\underline{H_2}$Cl); 3.93 (s, 3H, O—CH_3); 4.52 (s, 2H, C5—$C\underline{H_2}$—N); 4.74 (s, 2H, Bn); 5.42–6.48 (bs, 2H, 4-NH_2); 7.23–7.28 (m, 3H, two H_o and H_p Ph); 7.31–7.37 (m, 2H, two H_m Ph). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.6 p (N—CH_3); 36.0 s (CO—$C\underline{H_2}$); 39.8 s ($C\underline{H_2}$Cl); 41.0 s (C5—$C\underline{H_2}$—N); 51.3 s (Bn); 55.25 p (O—CH_3); 88.8 q (C5); 126.3 t (C_o Ph); 127.3 t (C_m Ph); 128.7 t (C_p Ph); 136. 8 q (C_i Ph); 155. 9 q (C2); 160.7 q (C4); 164.2 q (C6); 171.6 q (N—$C\underline{O}$). IR (KBr) ν (cm^{-1}): 3426 (m); 3337 (m); 3227 (w); 2949 (w); 1667 (s); 1641 (s); 1610 (s); 1592 (s); 1542 (s); 1475 (s); 1215 (m). MS (70 eV) *m/z* (%): 364 (M^+, 2); 273 (60); 183 (48); 168 (100); 91 (56). HR MS: calc for $C_{17}H_{21}N_4O_3Cl$ 364.1302; found 364.1303.

Crystal data for **10a** were deposited at CCDC with reference CCDC 1,037,316: Chemical formula $C_{17}H_{21}ClN_4O_3$, M_r 364.13, Triclinic, *P*-1, 120 K, cell dimensions *a, b, c* (Å) 8.1086 (8), 8.7520 (9), 13.5072 (11); *α, β, γ* (°) 102.742 (7), 95.910 (9) × 114.045 (8), *V* (Å^3) 833.57 (47), *Z* = 2, *F*(000) = 384, D_x (Mg m^{-3}) = 1.454, Mo *Kα*, μ (mm^{-1}) = 0.255, Crystal size (mm) = 0.31 × 0.19 × 0.17. Data collection: KappaCCD Diffractometer, Monochromator graphite, CCD rotation images, thick slices φ & θ scans, absorption correction *SADABS* 2.10, *T*min, *T*max 0.534, 0.756 No. of measured, independent and observed [$I > 2\sigma(I)$] reflections 21,260, 3825, 2721, *R*int = 0.044, *θ* values (°): *θ*max = 27.5, *θ*min = 3.2; Range $h = -10 \rightarrow 10$, $k = -11 \rightarrow 11$, $l = -17 \rightarrow 17$, Refinement on $F2$:$R[F2 > 2\sigma(F2)] = 0.047$, $wR(F2) = 0.109$, $S = 1.05$. No. of reflections 3825, No. of parameters 228, No. of restraints 0. Weighting scheme: $w = 1/\sigma^2(F_o^2) + (0.0534P)^2 + 0.6588P$ where $P = (F_o^2 + 2F_c^2)/3$. $(\Delta/\sigma) < 0.001$, $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3}) 0.28, −0.56.

*4.3.29. N-[(4-amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzyl-3-bromopropanamide (**10b**)*

From 0.274 g of **2b** and 0.100 ml of 3-bromopropionyl bromide. M.p. 168 – 9 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.89 (t, 6.7 Hz, 2H, CO—$C\underline{H_2}$—CH_2Cl); 3.28 (s, 3H, N—CH_3); 3.62 (t, 6.7 Hz, 2H, CO—CH_2—$C\underline{H_2}$Cl); 3.93 (s, 3H, O—CH_3); 4.52 (s, 2H, C5—$C\underline{H_2}$—N); 4.74 (s, 2H, Bn); 5.69–6.36 (bs, 2H, 4-NH_2); 7.23–7.29 (m, 3H, two H_o and H_p Ph); 7.30–7.36 (m, 2H, two H_m Ph). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.1 s (CO—$C\underline{H_2}$); 27.6 p (N—CH_3); 36.2 s ($C\underline{H_2}$Cl); 41.0 s (C5—$C\underline{H_2}$—N); 51.3 s (Bn); 55.3 p (O—CH_3); 88.7 q (C5); 126.3 t (C_o Ph); 127.3 t (C_m Ph); 128.7 t (C_p Ph); 136. 8 q (C_i Ph); 155. 9 q (C2); 160.7 q (C4); 164.3 q (C6); 171.9 q (N—$C\underline{O}$). IR (KBr) ν (cm^{-1}): 3395 (m); 3321 (m); 3203 (m); 3024 (w); 2953 (w); 2897 (w); 1656 (s, b); 1614 (s, b); 1542 (s, b); 1475 (s); 1211 (s). MS (70 eV) *m/z* (%): 408/410 (M/M + 2, 2/2); 319 (21); 273 (58); 182 (49); 168 (100); 111 (15); 90 (20). HR MS: calc for $C_{17}H_{21}N_4O_3Br$ 408.0797; found 408.0796.

*4.3.30. N-{[4-amino-(2-methylthio)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-N-benzyl-3-chloropropanamide (**10c**)*

From 0.290 g of **2e** and 0.090 ml of 3-chloropropionyl chloride. M.p. 158 – 60 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.50 (s, 3H, S—CH_3); 2.78 (t, 6.6 Hz, 2H, CO—$C\underline{H_2}$—CH_2Cl); 3.39 (s, 3H, N—CH_3); 3.79 (t, 6.6 Hz, 2H, CO—CH_2—$C\underline{H_2}$Cl); 4.53 (s, 2H, C5—$C\underline{H_2}$—N); 4.75 (s, 2H, Bn); 5.72–6.35 (bs, 2H, 4-NH_2); 7.22–7.29 (m, 2H, two H_o Ph); 7.29–7.37 (m, 3H, two H_m and H_p Ph). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.7 p (S—CH_3); 30.0 p (N—CH_3); 36.0 s (CO—$C\underline{H_2}$); 39.7 s ($C\underline{H_2}$Cl); 41.0 s

(C5—C$\underline{H_2}$—N); 51.4 s (Bn); 90.4 q (C5); 126.3 t (C_o Ph); 127.5 t (C_m Ph); 128.7 t (C_p Ph); 136. 7 q (C_i Ph); 159.9 q (C2); 161.6 q (C4); 163.6 q (C6); 171.6 q (N—C=O). IR (KBr) ν (cm^{-1}): 3346 (m, b); 3195 (m); 2932 (w); 1614 (s, b); 1536 (m); 1513 (m); 1452 (m); 1414 (m). MS (70 eV) *m/z* (%): 380 (M^+, 2); 289 (56); 253 (14); 199 (49); 184 (97); 91 (100). HR MS: calc for $C_{17}H_{21}N_4O_2SCl$ 380.1074; found 380.1076.

4.4. Indoline-pyrimidine hybrid by the reaction of [(6-amino-pyrimidin-5-yl)methyl](phenyl)amino with haloacyl halides

1-[(4-Amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimi din-5-yl)methyl]-3,3-diphenylindolin-2-one (**7**). From 0.260 g of 2a and 0.273 ml of 2-chloro-2,2-diphenylacetyl chloride according to 4.1.2. general procedure. The product is isolated by flash chromatography (silicagel, DCM/MeOH, 95:5). Yield: 57%. M.p. 228 – 9 °C. ^{1}H NMR (CDCl3). δppm: 3.37 (s, 3H, N-CH_3); 3.92 (s, 3H, O-CH_3); 4.86 (s, 2H, C5—C$\underline{H_2}$—N); 5.50–6.70. (bs, 2H, 4-NH_2); 7.06 (td, 1.0 Hz and 7.4 Hz, 1H, $H_{5'}$ in indolinone ring); 7.18 (dd, 1.2 and 7.4 Hz, 1H, $H_{7'}$ in indolinone ring); 7.20–7.30 (m, 10H, all Hs in two Ph rings); 7.33 (td, 1.4 and 7.8 Hz, 1H, $H_{6'}$ in indolinone ring); 7.83 (pd, 8 Hz, 1H, $H_{4'}$ in indolinone ring). ^{13}C NMR (CDCl3) δppm: 27.8 p (N—CH_3); 35.6 s (C5—C$\underline{H_2}$—N); 55.3 p (O—CH_3); 63.0 q (C3′ in indolinone); 86.9 q (C5); 111.8 t (C5′ indolinone); 123.2 t (C7′ in indolinone); 125.5 t (C6′ in indolinone); 127.3 t (C_p in two Ph); 128.4 t (C_o in two Ph); 128.4 t(C_m in two Ph); 128.8 t (C4′ in indolinone); 132.8 q (C3a′ in indolinone); 141.6 q (C_i in two Ph); 142.1 q (C7a′ in indolinone); 156.1 q (C2); 160.5 q (C4); 163.4 q (C6); 179.75 q (C(2′)=O). IR (KBr) ν (cm^{-1}): 3348 (s); 3029 (w); 2928 (w); 1671 (s); 1624 (m); 1601 (m); 1524 (s); 1445 (s). MS (70 eV) *m/z* (%): 452 (M+, 7); 424 (5); 285 (4); 168 (100); 111 (8). HR MS: calc for $C_{27}H_{24}N_4O_3$ 452.1848; found 452.1851.

*4.5. Cyclization of intermediates (6-aminopyrimidin-5-yl)methylamino acyl halides to pyrimido[4,5-e][1,4]diazepines (**8**)*

Method A: To a solution of acylated pyrimidine **5** (1 mmol) in dry DMF (4 mL) anhydrous potassium carbonate (1 mmol) was added, and the mixture was heated to 80–90 °C until the starting pyrimidine is not observed by TLC (AcOEt/hexane 8:2). The product was purified by column chromatography (AcOEt/hexane 1:1) if needed and recrystallized from hexane-EtOH (1:1).

Method B: 1 mmol of the starting pyrimidine (**3**) is solved in 4 ml of DMF anhydrous and placed in an ice bath. 0.05 g (1 mmol) of sodium hydride (60%) with continuous stirring until the starting pyrimidine disappears. The reaction is monitored by TLC (AcOEt/hexane 8:2). Then 10–15 ml of water is added to the reaction mixture and the solid in suspension is filtered and washed with cold water. The solid is recrystallized from hexane - EtOH.

*4.5.1. 2-Methoxy-3-methyl-6-phenyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8a**)*

Method A: From 0.336 g of **5a**; reaction time: 4 h 30 min; colourless solid (85%). Method B: From 0.336 g of **5a**; reaction time: 20 min; colourless solid (98%). M.p. 261 – 5 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.35 (s, 3H); 3.93 (s, 3H); 4.33 (d, 2H, 5.8 Hz); 4.98 (s, 2H); 5.11 (t, 5.8 Hz, 1H); 7.18–7.21 (m, 1H); 7.32–7.37 (m, 4H); ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.8 p; 45.7 s; 48.4, s; 55.4 p; 89.1 q; 125.2 t; 126.3 t; 128.9 t; 142.4 q; 155.7 q; 158.4 q; 162.0 q; 167.8 q. IR (KBr) ν (cm^{-1}): 3426 (m); 3337 (m); 3227 (w); 2949 (w); 1667 (s); 1641 (s); 1610 (s); 1592 (s); 1542 (s); 1475 (s); 1215 (m). MS (70 eV) *m/z* (%): 300 (M^+, 45); 196 (4); 180 (100); 152 (20); 108 (11); 80 (7); 72 (12). HR MS: calc for $C_{15}H_{16}N_4O_3$ 300.1222; found 300.1227.

*4.5.2. 2-Methoxy-3,8-dimethyl-6-phenyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8b**)*

Method A: From 0.350 g of **5b**; reaction time: 13 h; colourless solid (85%). Method B: From 0.350 g of **5b**; reaction time: 15 min; colourless solid (58%). M.p. 158 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.49 (d, 6.6 Hz, 3H); 3.34 (s, 3H); 3.93 (s, 3H); 4.56 (d, 3.7 Hz, 1H); 4.93 (d, 16.8 Hz, 1H); 4.92–5.01 (m, 1H); 5.03 (d, 16.8 Hz, 1H); 7.15–7.20 (m, 1H); 7.25–7.35 (m, 4H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 16.6 p; 27.8 p; 45.3 s; 49.3 t; 55.3 p; 89.1 q; 125.4 t; 126.2 t; 128.8 t; 142.9 q; 155.6 q; 158.1 q; 162.0 q; 169.3 q. IR (KBr) ν (cm^{-1}): 3336 (m, b); 2983 (w); 2936 (w); 1651 (s); 1611 (m); 1571 (s); 1517 (s); 1410 (m); 1197 (m). MS (70 eV) *m/z* (%): 314 (M^+, 33); 194 (68); 180 (100); 152 (10); 123 (12); 108 (6); 80 (11); 72 (23). HR MS: calc for $C_{16}H_{18}N_4O_3$ 314.1373; found 314.1371.

*4.5.3. 6-Benzyl-2-methoxy-3-methyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8d**)*

Method A: From 0.350 g of **5d**; reaction time: 3 h 45 min; colourless solid (70%). Method B: From 0.350 g of **5d**; reaction time: 50 min; colourless solid (84%). M.p. 217 – 9 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.28 (s, 3H); 3.89 (s, 3H); 4.20 (d, 5.6 Hz, 2H); 4.46 (s, 2H); 4.63 (s, 2H); 5.06 (t, 5.6 Hz, 1H); 7.25–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.7 p; 41.9 s; 47.55 s; 50.4 s; 55.3 p; 88.7 q; 127.4 t; 128.3 t; 128.5 t; 137.1 q; 155.4 q; 158.1 q; 162.2 q; 168.7 q. IR (KBr) ν (cm^{-1}): 3310 (m); 2942 (w, b); 1645 (s); 1612 (m); 1561 (s); 1518 (s); 1228 (m). MS (70 eV) *m/z* (%): 314 (M^+, 30); 223 (100); 195 (16); 180 (70); 152 (10); 123 (18); 91 (49); 80 (12); 72 (25). HR MS: calc for $C_{16}H_{18}N_4O_3$ 314.1379; found 314.1380.

*4.5.4. 6-Benzyl-2-methoxy-3,8-dimethyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8e**)*

Method A: From 0.364 g of **5e**; reaction time: 20 h; colourless solid (64%). Method B: From 0.364 g of **5e**; reaction time: 40 min; colourless solid (88%). M.p. 176 – 84 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.46 (d, 6.6 Hz, 3H); 3.27 (s, 3H); 3.90 (s, 3H); 4.26 (d, 14.5 Hz, 1H), 4.44–4.53 (m, 3H); 4.80 (dq, 3.9 Hz and 13.0 Hz, 1H); 5.02 (d, 14.7 Hz, 1H); 7.21–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 16.52 p; 27.64 p; 41.70 s; 48.72 t; 50.68 s; 55.25 p; 88.8 q; 127.3 t; 128.4 t; 128.4 t; 137.4 q; 155.3 q; 157.8 q; 162.2 q; 170.1 q. IR (KBr) ν (cm^{-1}): 3305 (m); 2995 (w); 2929 (w); 1671 (s); 1642 (s); 1605 (m); 1553 (s); 1520 (s, b); 1447 (m); 1414 (m); 1225 (m); 1193 (m). MS (70 eV) *m/z* (%): 328 (M^+, 52); 223 (85); 194 (67); 180 (100); 123 (10); 123 (18); 91 (25); 80 (7); 72 (18). HR MS: calc for $C_{17}H_{20}N_4O_3$ 328.1535; found 328.1537.

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*4.5.5. 6-Benzyl-2-methoxy-3-methyl-8-phenyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8f**)*

Method A: From 0.427 g of **5f**; reaction time: 3 h; colourless solid (64%). Method B: From 0.427 g of **5f**; reaction time: 15 min; colourless solid (82%). M.p. 232 – 4 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.29 (s, 3H); 3.75 (d, 16.7 Hz, 1H); 3.95 (s, 3H); 4.27 (d, 16.7 Hz, 1H); 4.42 (d, 14.6 Hz, 1H); 4.87 (d, 14.6 Hz, 1H); 5.40 (d, 6.7 Hz, 1H); 5.49 (d, 6.7 Hz, 1H), 7.22–7.41 (m, 10H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.7 p; 40.4 s; 51.2 s; 55.3 p; 62.1 t; 89.2 q; 125.3 t; 127.3 t; 128.1 t; 128.2 t; 128.4 t; 129.0 t; 137.1 q; 137.9 q; 155.4 q; 157.5 q; 162.1 q; 169.05 q. IR (KBr) ν (cm^{-1}): 3299 (m); 2954 (w, b); 1687 (m); 1642 (s); 1613 (m); 1569 (s); 1519 (s); 1450 (m); 1236 (m); 1195 (m). MS (70 eV) *m/z* (%): 390 (M^+, 7); 257 (100); 242 (21); 180 (9); 91 (16); 80 (3). HR MS: calc for $C_{22}H_{22}N_4O_3$ 390.1692; found 390.1685.

*4.5.6. 6-Benzyl-8-ethyl-2-methoxy-3-methyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8h**)*

Method A: From 0.424 g of **5h**; reaction time: 3 h 30 min; colourless solid (38%). M.p. 161 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.10 (t, 7.4 Hz, 3H); 1.62–1.71 (m, 1H); 2.07–2.17 (m, 1H); 3.27 (s, 3H); 3.90 (s, 3H); 4.28 (d, 14.6 Hz, 1H); 4.44 (d, 16.8 Hz, 1H); 4.46–4.53 (m, 2H); 4.52 (d, 16.8 Hz, 1H); 5.00 (d, 14.6 Hz, 1H); 7.21–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 10.8 p; 24.1 s; 27.6 p; 41.7 s; 50.5 s; 54.8 t; 55.3 p; 88.8 q; 127.3 t; 128.35 t; 128.4 t; 137.4 q; 155.3 q; 157.9 q; 162.2 q; 169.6 q. IR (KBr) ν (cm^{-1}): 3262 (m); 2972 (d, a); 2879 (d); 1665 (f); 1640 (f, a); 1567 (f); 1513 (f); 1443 (m); 1224 (m). MS (70 eV) *m/z* (%): 342 (M^+, 42); 251 (51); 194 (20); 180 (100); 123 (6); 91 (19); 72 (12). HR MS: calc for $C_{18}H_{22}N_4O_3$ 342.1692; found 342.1690.

*4.5.7. 6-Benzyl-8-butyl-2-methoxy-3-methyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8i**)*

Method A: From 0.452 g of **5i**; reaction time: 3 h; colourless solid (55%). Method B: From 0.452 g of **5i**; reaction time: 30 min; colourless solid (95%). M.p. 153 – 5 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 0.95 (t, 7.0 Hz, 3H); 1.39–1.46 (m, 4H); 1.62–1.69 (m, 1H); 2.05–2.14 (m, 1H); 3.27 (s, 3H); 3.90 (s, 3H); 4.29 (d, 14.5 Hz, 1H); 4.44 (d, 16.8 Hz, 1H); 4.47–4.59 (m, 1H); 4.52 (d, 16.8 Hz, 1H); 4.47–4.59 (m, 1H); 4.98 (d, 14.5 Hz, 1H); 7.22–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 13.9 p; 22.6 s; 27.6 p; 28.2 s; 30.6 s; 41.8 s; 50.6 s; 53.3 p; 55.3 p; 88.8 q; 127.3 t; 128.4 t; 128.4 t; 137.4 q; 155.3 q; 157.9 q; 162.2 q; 169.8 q. IR (KBr) ν (cm^{-1}): 3252 (m, b); 2957 (w); 2930 (w); 2873 (w); 1665 (m); 1643 (s); 1607 (m); 1564 (m, b); 1515 (s). MS (70 eV) *m/z* (%): 370 (M^+, 41); 279 (59); 237 (43); 208 (31); 194 (24); 180 (100); 168 (46); 91 (39); 72 (22). HR MS: calc for $C_{20}H_{26}N_4O_3$ 370.2005; found 370.1996.

*4.5.8. 6-Cyclohexyl-2-methoxy-3-methyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8k**)*

Method A: From 0.343 g of **5k**; reaction time: 3 h; colourless solid (75%). Method B: From 0.343 g of **5k**; reaction time: 30 min; colourless solid (57%). M.p. 258 – 60 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.16 (qt, 3.3 Hz and 12.8 Hz, 1H); 1.35 (qt, 3.3 Hz and 12.8 Hz, 2H); 1.48 (qd, 3.3 Hz and 12.4 Hz, 2H); 1.57–1.66 (m, 3H); 1.73–1.80 (m, 2H); 3.32 (s, 3H); 3.90 (s, 3H); 4.16 (d, 5.5 Hz, 2H); 4.39 (tt, 3.7 Hz and 11.8 Hz, 1H); 4.45 (s, 2H); 4.99 (t, 5.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 25.2 s; 25.6 s; 27.7 p; 30.2 s; 36.4 s; 47.9 s; 52.8 t; 55.2 p; 89.5 q; 155.4 q; 158.3 q; 161.7 q; 168.2 q. IR (KBr) ν (cm^{-1}): 3295 (s); 2942 (m); 2862 (w); 2847 (w); 1635 (w, b); 1562 (w); 1524 (w); 1482 (w); 1416 (m); 1227 (m). MS (70 eV) *m/z* (%): 306 (M^+, 51); 224 (44); 180 (100); 152 (14); 123 (14); 98 (8); 72 (11). HR MS: calc for $C_{15}H_{22}N_4O_3$ 306.1692; found 306.1698.

*4.5.9. 6-Cyclohexyl-2-methoxy-3,8-dimethyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8l**)*

Method A: From 0.357 g of **5l**; reaction time: 5 h 30 min; colourless solid (62%). Method B: From 0.357 g of **5l**; reaction time: 30 min; after the addition of water (15 ml) the solution is extracted with AcOEt (30 ml ×3) dried with Na_2SO_4 and after filtration of the solid the solvent is evaporated. Colourless foam (90%). M.p. 127 – 33 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.16 (qt, 3.30 Hz and 12.9 Hz, 1H); 1.25–1.36 (m, 3H); 1.42 (d, 6.6 Hz, 3H); 1.46–1.85 (m, 6H); 3.32 (s, 3H); 3.89 (s, 3H); 4.36 (d, 16.8 Hz, 1H); 4.42–4.48 (m, 1H); 4.57 (d, 16.8 Hz, 1H); 4.78 (dq, 3.9 Hz and 12.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 16.6 p; 25.2 s; 25.6 s; 27.7 p; 30.2 s; 30.4 s; 36.1 s; 48.9 t; 53.0 t; 55.2 p; 89.7 q; 155.3 q; 157.9 q; 161.7 q; 169.4 q. IR (KBr) ν (cm^{-1}): 3263 (m, b); 2926 (m); 2854 (m); 1669 (s); 1640 (s, b); 1611 (s); 1564 (s); 1521 (s); 1415 (m); 1226 (m); 1174 (m). MS (70 eV) *m/z* (%): 320 (M^+, 35); 238 (7); 195 (87); 180 (100); 152 (9); 98 (6); 80 (6); 72 (16). HR MS: calc for $C_{16}H_{24}N_4O_3$ 320.1848; found 320.1837.

*4.5.10. 3-methyl-2-(methylthio)-6-phenyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8n**)*

Method A: From 0.353 g of **5n**; reaction time: 6 h; colourless solid (70%). Method B: From 0.353 g of **5n**; reaction time: 20 min; colourless solid (64%). M.p. 214 – 6 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.47 (s, 3H); 3.45 (s, 3H); 4.33 (d, 5.6 Hz, 2H); 4.99 (s, 2H); 5.21 (t, 5.6 Hz, 1H); 7.17–7.22 (m, 1H); 7.30–7.37 (m, 4H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 30.2 p; 45.5 s; 48.3 s; 90.7 q; 125.2 t; 126.4 t; 128.9 t; 142.3 q; 157.7 q; 161.2 q; 161.7 q; 167.7 q. IR (KBr) ν (cm^{-1}): 3318 (m); 2914 (w); 1667 (s); 1618 (s, b); 1580 (s); 1547 (m); 1508 (m); 1411 (m). MS (70 eV) *m/z* (%): 316 (M^+, 71); 197 (99); 182 (37); 164 (15); 150 (100); 122 (48); 88 (54); 80 (20); 77 (20). HR MS: calc for $C_{15}H_{16}N_4O_2S$ 316.0994; found 316.1001.

*4.5.11. 3,8-dimethyl-2-(methylthio)-6-phenyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8o**)*

Method A: From 0.366 g of **5o**; reaction time: 4 h; colourless solid (90%). Method B: From 0.366 g of **5o**; reaction time: 15 min; colourless solid (94%). M.p. 140 – 50 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.50 (d, 6.6 Hz, 3H); 2,49 (s, 3H); 3.45 (s, 3H); 4.66 (d, 3.7 Hz, 1H); 4.94 (d, 16.9 Hz, 1H); 4.93–5.00 (m, 1H); 5.05 (d, 16.9 Hz, 1H); 7.19 (pt, 7.2 Hz, 1H); 7.26–7.36 (m, 4H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 16.5 p; 30.2 p; 45.2 s; 49.2 t; 90.7 q; 125.4 t; 126.3 t; 128.8 t; 142.8 q; 157.4 q; 161.2 q; 161.5 q; 169.2 q. IR (KBr) ν (cm^{-1}): 3420 (m, b); 3357 (m); 3277 (m, b); 2988 (w); 2928 (w); 1676 (m); 1627 (s); 1586 (s); 1531 (s, b); 1496 (s); 1412 (m). MS (70 eV) *m/z* (%): 330 (M^+, 48); 210 (71); 196 (100); 184 (12); 164 (38); 136 (22); 88 (54); 77 (14). HR MS: calc for $C_{16}H_{18}N_4O_2S$ 330.1150; found 330.1144.

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*4.5.12. 6-Benzyl-3-methyl-2-(methylthio)-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8q**)*

Method A: From 0.367 g of **5q**; reaction time: 1 h 30 min; colourless solid (80%). Method B: From 0.367 g of **5q**; reaction time: 30 min; colourless solid (77%). M.p. 221 – 3 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.45 (s, 3H); 3.38 (s, 3H); 4.21 (d, 5.5 Hz, 2H); 4.48 (s, 2H); 4.63 (s, 2H); 5.14 (t, 5.5 Hz, 1H); 7.24–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 30.1 p; 41.7 s; 47.5 s; 50.4 s; 90.4 q; 127.4 t; 128.3 t; 128.5 t; 137.0 q; 157.5 q; 161.2 q; 161.4 q; 168.7 q. IR (KBr) ν (cm^{-1}): 3319 (m); 3059 (w); 3031 (w); 2929 (w); 1664 (s); 1627 (s); 1587 (s); 1541 (s); 1506 (s); 1428 (m); 1225 (m). MS (70 eV) *m/z* (%): 330 (M^+, 42); 239 (100); 196 (44); 182 (12); 150 (43); 139 (22); 122 (14); 91 (61); 88 (42); 80 (12). HR MS: calc for $C_{16}H_{18}N_4O_2S$ 330.1150; found 330.1146.

*4.5.13. 6-Benzyl-3,8-dimethyl-2-(methylthio)-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8r**)*

Method A: From 0.380 g of **5r**; reaction time: 14 h; colourless solid (84%). Method B: From 0.380 g of **5r**; reaction time: 30 min; colourless solid (86%). M.p. 189 – 90 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.47 (d, 6.6 Hz, 3H); 2.46 (s, 3H); 3.38 (s, 3H); 4.28 (d, 14.5 Hz, 1H); 4.50–4.55 (m, 3H), 4.77–4.82 (m, 1H); 5.01 (d, 14.5 Hz, 1H); 7.23–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 16.5 p; 30.1 p; 41.6 s; 48.7 t; 50.7 s; 90.5 q; 127.3 t; 128.4 t; 128.4 t; 137.3 q; 157.2 q; 161.1 q; 161.4 q; 170.0 q. IR (KBr) ν (cm^{-1}): 3246 (m, b); 3001 (w); 2924 (w); 1656 (s); 1627 (s, b); 1582 (s); 1537 (s, b); 1509 (s, b); 1420 (m). MS (70 eV) *m/z* (%): 344 (M^+, 73); 253 (95); 239 (18); 210 (64); 196 (100); 164 (33); 91 (38); 88 (50). HR MS: calc for $C_{17}H_{20}N_4O_2S$ 344.1307; found 344.1311.

*4.5.14. 6-Benzyl-3-methyl-2-(methylthio)-8-phenyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8s**)*

Method A: From 0.442 g of **5s**; reaction time: 1 h; colourless solid (87%). M.p. 239 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.51 (s, 3H); 3.40 (s, 3H); 3.76 (d, 16.7 Hz, 1H); 4.28 (d, 16.7 Hz, 1H); 4.41 (d, 14.7 Hz, 1H); 4.88 (d, 14.7 Hz, 1H); 5.50 (sa, 2H); 7.20–7.30 (m, 5H); 7.30–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.7 p; 30.1 p; 40.3 s; 51.2 s; 62.0 t; 90.9 q; 125.3 t; 127.3 t; 128.1 t; 128.2 t; 128.4 t; 129.0 t; 137.0 q; 137.8 q; 156.9 q; 161.2 q; 161.3 q; 169.0 q. IR (KBr) ν (cm^{-1}): 3314 (m); 3029 (w); 2927 (w); 1645 (s); 1628 (s) 1591 (s); 1540 (s); 1507 (s); 1414 (m). MS (70 eV) *m/z* (%): 406 (M^+, 6); 290 (47); 273 (100); 258 (25); 198 (15); 170 (17); 91 (11). HR MS: calc for $C_{22}H_{22}N_4O_2S$ 406.1463; found 406.1468.

*4.5.15. 6-Benzyl-8-ethyl-3-methyl-2-(methylthio)-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8u**)*

Method A: From 0.439 g of **5u**; reaction time: 1 h & 20 min; colourless solid (91%). M.p. 172 – 3 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.10 (t, 7.4 Hz, 3H); 1.65–1.72 (m, 1H); 2.10–2.17 (m, 1H); 2.47 (s, 3H); 3.37 (s, 3H), 4.31 (d, 14.7 Hz, 1H); 4.46 (d, 17.1 Hz, 1H); 4.45–4.55 (m, 2H); 4.54 (d, 17.1 Hz, 1H); 4.97 (d, 14.7 Hz, 1H); 7.21–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 10.8 p; 14.6 p; 24.1 s; 30.1 p; 41.6 s; 50.6 s; 54.7 t; 90.5 q; 127.3 t; 128.3 t; 128.4 t; 137.4 q; 157.3 q; 161.0 q; 161.5 q; 169.5 q. IR (KBr) ν (cm^{-1}): 3340 (m); 2979 (w); 2928 (w); 1658 (s); 1632 (s); 1580 (s); 1537 (s); 1501 (s); 1431 (m). MS (70 eV) *m/z* (%): 358 (M^+, 20); 267 (37); 225 (29); 196 (100); 184 (12); 170 (61); 124 (20); 91 (15). HR MS: calc for $C_{18}H_{22}N_4O_2S$ 358.1463; found 358.1469.

Crystal data for **8u** were deposited at CCDC with reference CCDC 1,037,315: Chemical formula $C_{18}H_{22}N_4O_2S$, M_r 358.15, Monoclinic, *P*21/c, 120 K, cell dimensions *a, b, c* (Å) 7.7280 (8), 26.421 (2), 8.3554 (10); *α, β, γ* (°) 90, 102.392 (10), 90. *V* (Å^3) 1666.2 (3), *Z* = 4, *F*(000) = 760, D_x (Mg m^{-3}) = 1.429, Mo *Kα*, *μ* (mm^{-1}) = 0.215, Crystal size (mm) = 0.47 × 0.32 × 0.18. Data collection: Diffractometer KappaCCD, Monochromator graphite, CCD rotation images, thick slices φ & θ scans, absorption correction *SADABS* 2.10, *T*min, *T*max 0.503, 0.756. No. of measured, independent and observed [$I > 2\sigma(I)$] reflections 20,117, 3792, 2201, *R*int = 0.061, *θ* values (°): *θ*max = 27.5, *θ*min = 2.8; Range $h = -10 \rightarrow 9$, $k = -34 \rightarrow 32$, $l = -10 \rightarrow 10$, Refinement on *F*2:*R*[$F2 > 2\sigma(F2)$] = 0.055, *wR*(*F*2) = 0.118, *S* = 1.05. No. of reflections 3792, No. of parameters 229, No. of restraints 0. Weighting scheme: $w = 1/[\sigma^2(F_o^2) + (0.0589P)^2 + 1.596P]$ where $P = (F_o^2 + 2F_c^2)/3$. $(\Delta/\sigma) < 0.001$, $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3}) 0.47, −0.41.

*4.5.16. 6-Benzyl-8-butyl-3-methyl-2-(methylthio)-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8v**)*

Method A: From 0.467 g of **5v**; reaction time: 1 h; colourless solid (93%). M.p. 172 – 3 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 0.95 (t, 7.0 Hz, 3H); 1.35–1.48 (m, 4H); 1.60–1.67 (m, 1H); 2.05–2.17 (m, 1H); 2.47 (s, 3H); 3.37 (s, 3H); 4.31 (d, 14.5 Hz, 1H); 4.46 (d, 17.4 Hz, 1H); 4.50–4.60 (m, 3H); 4.97 (d, 14.5 Hz, 1H); 7.20–7.33 (m, 5.0 Hz). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 13.9 p; 14.6 p; 22.6 s; 28.3 s; 30.3 p; 30.6 s; 41.7 s; 50.6 s; 53.2 t; 90.5 q; 127.3 t; 128.3 t; 128.4 t; 137.4 q; 157.3 q; 161.0 q; 161.4 q; 169.9 q. IR (KBr) ν (cm^{-1}): 3271 (m); 2955 (w); 2928 (w); 2856 (w); 1632 (s, b); 1584 (m); 1529 (s); 1513 (s, b); 1410 (m); 1351 (w). MS (70 eV) *m/z* (%): 386 (M^+, 34); 295 (42); 253 (36); 224 (29); 196 (100); 91 (15); 88 (71). HR MS: calc for $C_{20}H_{26}N_4O_2S$ 386.1776; found 386.1768.

*4.5.17. 6-Cyclohexyl-3-methyl-2-(methylthio)-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8w**)*

Method A: From 0.359 g of **5w**; reaction time: 1 h & 30 min; colourless solid (56%). Method B: From 0.359 g of **5w**; reaction time: 15 min; colourless solid (57%). M.p. 242 – 5 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.15 (qt, 3.3 Hz and 12.8 Hz, 1H); 1.34 (qt, 3.3 Hz and 12.8 Hz, 2H); 1.45 (qd, 3.3 Hz and 12.4 Hz, 2H); 1.57–1.67 (m, 3H); 1.77 (pd, 13.0 Hz, 2H); 2.46 (s, 3H); 3.43 (s, 3H); 4.17 (d, 5.5 Hz, 2H); 4.39 (tt, 3.7 Hz and 11.8 Hz, 1H); 4.47 (s, 2H); 5.09 (t, 5.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 25.2 s; 25.6 s; 30.1 p; 30.2 s; 36.3 s; 47.8 s; 52.8 t; 91.2 q; 157.6 q; 161.0 q; 161.1 q; 168.1 q. IR (KBr) ν (cm^{-1}): 3323 (f); 2940 (f); 2857 (m); 1652 (f); 1622 (f); 1582 (f); 1538 (f, a); 1481 (f); 1454 (f). MS (70 eV) *m/z* (%): 322 (M^+, 73); 240 (61); 196 (100); 182 (31); 150 (84); 122 (36); 98 (30); 88 (16); 80 (18). HR MS: calc for $C_{15}H_{22}N_4O_2S$ 322.1463; found 322.1457.

*4.5.18. 6-Cyclohexyl-3,8-dimethyl-2-(methylthio)-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8x**)*

Method A: From 0.373 g of **5x**; reaction time: 2 h & 15 min; colourless solid (90%). Method B: From 0.373 g of **5x**; reaction time: 30 min; colourless solid (88%). M.p. 184 – 5 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.25–1.40 (m, 3H); 1.43 (d, 6.6 Hz,

3H); 1.52–1.82 (m, 7H); 2.46 (s, 3H); 3.43 (s, 3H); 4.38 (d, 16.8 Hz, 1H); 4.45 (tt, 3.9 Hz and 11.8 Hz, 1H); 4.49 (d, 3.9 Hz, 1H); 4.59 (d, 16.8 Hz, 1H); 4.75–4.81 (m, 1H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.6 p; 16.6 p; 25.2 s; 25.6 s; 25.7 s; 30.2 p; 30.2 s; 30.5 s; 36.0 s; 48.9, t; 53.1 t; 91.4 q; 157.4 q; 161.0 q; 169.3 q. IR (KBr) ν (cm^{-1}): 3339 (m); 2941 (m); 2926 (m); 2853 (w); 1657 (s); 1625 (s); 1586 (s); 1534 (s); 1500 (s); 1414 (m). MS (70 eV) *m*/*z* (%): 336 (M^+, 60); 225 (12), 211 (100); 196 (88); 164 (28); 88 (16); 80 (8). HR MS: calc for $C_{16}H_{24}N_4O_2S$ 336.1620; found 336.1620.

*4.5.19. 6-Cyclohexyl-3-methyl-2-(methylthio)-8-phenyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**8y**)*

Method B: From 0.435 g of **5y**; reaction time: 20 min; colourless solid (90%). M.p. 237 – 41 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.00–1.20 (m, 1H); 1.25–1.50 (m, 4H); 1.65–1.80 (m, 5H); 2.52 (s, 3H); 3.44 (s, 3H); 3.61 (d, 16.9 Hz, 1H); 4.32 (d, 16.9 Hz, 1H); 4.41–4.47 (m, 1H); 5.41–5.46 (m, 2H); 7.30–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.7 p; 25.2 s; 25.5 s; 25.6 s; 29.9 s; 30.1 s; 30.1 p; 34.5 s; 53.4 t; 62.5 t; 91.6 t; 125.1 t; 128.0 t; 129.0 t; 138.4 q; 157.1 q; 160.9 q; 161.1 q; 168.4 q. IR (KBr) ν (cm^{-1}): 3293 (m, b); 2927 (m); 2854 (m); 1629 (s, b); 1602 (s); 1593 (s); 1525 (s, b); 1449 (m); 1413 (m). MS (70 eV) *m*/*z* (%): 398 (M^+, 3); 273 (100), 253 (23); 198 (12); 170 (17); 88 (16). HR MS: calc for $C_{21}H_{26}N_4O_2S$ 398.1776; found 398.1777.

4.6. Acylamide-pyrimidine hybrid by the elimination reaction from (6-aminopyrimidin-5-yl)methylamino acyl halides

*4.6.1. N-[(4-amino-2-methoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzylmethacrylamide (**9a**)*

Method A: From 0.423 g of **5j**; reaction time: 6 h & 30 min; colourless solid (58%). M.p. 146 – 8 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.90 (s, 3H); 3.28 (s, 3H); 3.93 (s, 3H); 4.47 (s, 2H); 4.77 (s, 2H); 5.07 (s, 1H); 5.12 (s, 1H); 6.04 (bs, 2H); 7.22–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 20.7 p; 27.6 p; 39.5 s; 52.5 s; 55.2 p; 89.0 q; 115.4 s; 127.1 t; 127.2 t; 128.4 t; 137.6 q; 140.2 q; 155.9 q; 160.8 q; 164.2 q; 174 .3 q. IR (KBr) ν (cm^{-1}): 3325 (m, b); 3185 (m); 2951 (w); 1643 (s, b); 1611 (s); 1583 (s); 1558 (s); 1474 (s); 1454 (s). MS (70 eV) *m*/*z* (%): 342 (M^+, 3); 273 (46); 251 (48); 168 (100); 111 (8); 91 (17). HR MS: calc for $C_{18}H_{22}N_4O_3$ 342.1692; found 342.1695.

*4.6.2. N-[(4-amino-1-methyl-2-methoxy-6-oxo-1,6-dihydropyrimidin-5-yl)methyl]-N-benzylacrylamide (**9b**)*

Method A: From 0.365 g of **10a**; reaction time: 1 h & 30 min; colourless solid (90%). Method B: From 0.365 g of **10a**; reaction time: 2 h; colourless solid (62%). Method B: From 0.409 g of **10b**; reaction time: 50 min; colourless solid (73%). M.p. 167 – 8 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.29 (s, 3H); 3.93 (s, 3H); 4.54 (s, 2H); 4.80 (s, 2H); 5.67 (dd, 2.1 and 10.0 Hz, 1H); 5.7–6.5 (bs); 6.39 (dd, 2.1 and 16.2 Hz, 1H); 6.55 (dd, 10.0 and 16.2 Hz, 1H); 7.25–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 27.6 p; 40.8 s; 51.1 s; 55.2 p; 88.7 q; 126.6 t; 127.3 t; 127.6 t; 128.6 t; 128.8 s; 137.3 q; 155.9 q; 160.9 q; 164.3 q; 167.9 q. IR (KBr) ν (cm^{-1}): 3326 (m, b); 3182 (m); 2954 (w); 1642 (s, b); 1604 (m); 1578 (s); 1559 (s); 1538 (m); 1483 (m). MS (70 eV) *m*/*z* (%): 328 (M^+, 9); 273 (60); 237 (78); 183 (57); 168 (100); 111 (24); 91 (29). HR MS: calc for $C_{17}H_{20}N_4O_3$ 328.1535; found 328.1539.

*4.6.3. N-{[4-amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl]methyl}-N-benzylacrylamide (**9c**)*

Method A: From 0.380 g of **10c**; reaction time: 2 h; colourless solid (80%). M.p. 175 – 7 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 2.49 (s, 3H); 3.40 (s, 3H); 4.55 (s, 2H); 4.80 (s, 2H); 5.68 (dd, 2.1 and 10.0 Hz, 1H); 5.7-6.5 (bs); 6.39 (dd, 2.1 and 16.2 Hz, 1H); 6.55 (dd, 10.0 and 16.2 Hz, 1H); 7.25–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ_{ppm}: 14.7 p; 30.0 p; 40.8 s; 51.2 s; 90.4 q; 126.5 t; 127.3 t; 127.5 t; 128.6 t; 128.9 s; 137.2 q; 160.0 q; 161.6 q; 163.6 q; 168.0 q. IR (KBr) ν (cm^{-1}): 3340 (m, b); 3191 (m); 2933 (w); 1639 (s); 1615 (s, b); 1536 (m); 1511 (m); 1453 (m); 1414 (m). MS (70 eV) *m*/*z* (%): 344 (M^+, 12); 289 (46); 253 (73); 199 (55); 184 (100); 91 (42). HR MS: calc for $C_{17}H_{20}N_4O_2S$ 344.1307; found 344.1308.

*4.7. Derivatization (N-Methylation) of pyrimido[4,5-e][1,4]diazepines (**8**)*

A equimolar amount of sodium hydride was added to a solution of pyrimido[4,5-*e*][1,4]diazepine (**8**) (1 mmol) (or its precursor haloacyl intermediate **5**) in DMF (2 mL) at 0 °C and stirred vigorously for 15 min, afterwards methyl iodide was added dropwise (1.6 mmol), and then stirred at 0 °C until no starting product was observed, by TLC monitoring (AcOEt/hexane 8:2). Then, water (10 mL) is poured into the solution and the mixture is stirred. The solid under suspension is filtered and recrystallized from EtOH – Hexane. If no solid is formed the product is extracted with AcOEt (10 ml x 3). The combined organic phases are dried under anhydrous sodium sulphate and the solvent removed under reduced pressure. The remaining solid was then recrystallized from EtOH – hexane.

*4.7.1. 2-Methoxy-3,8,9-trimethyl-6-phenyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**11a**)*

From 0.350 g of **5b**. Reaction time 35 min. Yellow solid (73%). M.p. 162 – 3 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.56 (d, 7.0 Hz, 3H); 3.13 (s, 3H); 3.35 (s, 3H); 3.98 (s, 3H); 4.92 (q, 7.0 Hz, 1H); 4.94 (d, 14.5 Hz, 1H); 4.98 (d, 14.5 Hz, 1H); 7.17 (pt, 7.2 Hz, 1H); 7.23–7.35 (m, 4H). ^{13}C NMR ($CDCl_3$). δ_{ppm}: 14.1 p; 27.7 p; 31.2 p; 47.6 s; 54.1 t; 55.1 p; 91.6 q; 125.5 t; 126.1 t; 128.8 t; 142.7 q; 154.5 q; 159.9 q; 162.6 q; 168.8 q. IR (KBr) ν (cm^{-1}): 2988 (w); 2944 (w); 2921 (w); 2870 (w); 1680 (s); 1633 (s, b); 1594 (m); 1572 (s); 1530 (s); 1493 (m); 1412 (m). MS (70 eV) *m*/*z* (%): 328 (M^+, 22); 285 (14), 223 (22); 208 (30); 194 (100); 104 (12); 72 (13). HR MS: calc for $C_{17}H_{20}N_4O_3$ 328.1535; found 328.1535.

*4.7.2. 6-Benzyl-2-methoxy-3,9-dimethyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**11b**)*

From 0.350 g of **5e**. Reaction time: 35 min. Yellow solid (70%). M.p. 143 – 6 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 3.20 (s, 3H); 3.22 (s, 3H); 3.88 (s, 3H); 4.17 (s, 2H); 4.40 (s, 2H); 4.54 (s, 2H); 7.18–7.24 (m, 5H). ^{13}C NMR ($CDCl_3$). δ_{ppm}: 27.7 p; 39.0 p; 43.4 s; 50.2 s; 55.1 p; 55.5 s; 89.7 q; 127.4 t; 128.3 t; 128.5 t; 137.1 q; 154.5 q; 158.5 q; 162.4 q; 168.2 q. IR (KBr) ν (cm^{-1}): 3006 (w); 2929 (w, b); 2859 (w); 1670 (s); 1647 (s, b); 1598 (s); 1546 (s); 1500 (m); 1477 (m); 1400 (m). MS (70 eV) *m*/*z* (%): 328 (M^+, 46); 237 (100); 209 (18); 194 (72); 182 (10); 122 (11); 91 (21); 72 (12). HR MS: calc for $C_{17}H_{20}N_4O_3$ 328.1535; found 328.1534.

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*4.7.3. 6-Benzyl-2-methoxy-3,8,9-trimethyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**11c**)*

From 0.364 g of **5f**. Reaction time: 25 min. Yellow solid (58%). M.p. 131 – 3 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.52 (d, 7.0 Hz, 3H); 3.09 (s, 3H); 3.29 (s, 3H); 3.95 (s, 3H); 4.42 (d, 17.3 Hz, 1H); 4.43 (d, 14.4 Hz, 1H); 4.47 (d, 17.0 Hz, 1H); 4.73 (q, 7.0 Hz, 1H); 4.80 (d, 14.4 Hz, 1H); 7.20–7.27 (m, 5H). ^{13}C NMR ($CDCl_3$). δ_{ppm}: 14.1 p; 27.6 p; 31.5 p; 44.2 s; 50.8 s; 53.9 t; 55.0 p; 91.2 q; 127.2 t; 128.1 t; 128.4 t; 137.4 q; 154.2 q; 159.6 q; 162.7 q; 169.8 q. IR (KBr) ν (cm^{-1}): 3023 (w); 2952 (w, b); 1652 (s, b); 1598 (s); 1548 (s, b); 1481 (m); 1452 (m); 1397 (m). MS (70 eV) *m/z* (%): 342 (M^+, 27); 223 (47); 208 (44); 194 (100); 91 (21); 72 (18). HR MS: calc for $C_{18}H_{22}N_4O_3$ 342.1692; found 342.1688.

*4.7.4. 6-Cyclohexyl-2-methoxy-3,9-dimethyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**11d**)*

From 0.306 g of the pyrimido-diazepine **8k**. Reaction time: 20 min. Colourless solid (81%). M.p. 151 – 2 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.14 (qt, 3.3 & 12.8 Hz, 1H);1.33 (qt, 3.3 & 12.8 Hz, 2H); 1.44 (qd, 3.3 & 11.9 Hz, 2H); 1.56–1.65 (m, 3H); 1.75 (pd, 12.8 Hz, 2H); 3.24 (s, 3H); 3.33 (s, 3H); 3.95 (s, 3H); 4.21 (s, 2H); 4.36 (tt, 3.7 & 11.9 Hz, 1H); 4.46 (s, 2H). ^{13}C NMR ($CDCl_3$). δ_{ppm}: 25.1 s; 25.5 s; 27.7 p; 30.2 s; 37.8 s; 39.0 p; 52.6 t; 55.0 p; 55.9 s; 90.5 q; 154.5 q; 158.6 q; 162.0 q; 167.6 q. IR (KBr) ν (cm^{-1}): 2923 (m, b); 2854 (m); 1640 (s, b); 1559 (s); 1548 (s, b); 1506 (m); 1406 (m). MS (70 eV) *m/z* (%): 320 (M^+, 37); 237 (14); 209 (11); 194 (100); 166 (13); 122 (6); 72 (5). HR MS: calc for $C_{16}H_{24}N_4O_3$ 320.1848; found 320.1851.

*4.7.5. 6-Cyclohexyl-2-methoxy-3,8,9-trimethyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**11e**)*

From 0.356 g of **5l**. Reaction time: 30 min. Colourless solid (47%). M.p. 162 – 5 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.06–1.19 (m, 1H); 1.26–1.41 (m, 3H); 1.48 (d, 6.9 Hz, 3H); 1.56–1.82 (m, 6H); 3.06 (s, 3H); 3.35 (s, 3H); 3.95 (s, 3H); 4.34 (d, 17.1 Hz, 1H); 4.39 (tt, 3.9 & 11.8 Hz, 1H); 4.53 (d, 17.1 Hz, 1H); 4.72 (q, 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$). δ_{ppm}: 14.2 p; 25.2 s; 25.5 s; 27.7 p; 29.7 s; 30.1 s; 30.7 s; 31.4 p; 38.1 s; 52.7 t; 54.1 t; 55.0 p; 92.2 q; 154.3 q; 159.8 q; 162.5 q; 168.9 q. IR (KBr) ν (cm^{-1}): 2998 (w); 2954 (m); 2926 (s); 2854 (m); 1643 (s, b); 1603 (m); 1546 (s, b); 1473 (m); 1450 (m, b). MS (70 eV) *m/z* (%): 334 (M^+, 13); 208 (27); 194 (100); 72 (18). HR MS: calc for $C_{17}H_{26}N_4O_3$ 334.2005; found 334.2002.

*4.7.6. 3,8,9-trimethyl-2-(methylthio)-6-phenyl-5,6,8,9-tetrahydro-3H-pyrimido[4,5-e][1,4]diazepine-4,7-dione (**11f**)*

From 0.350 g of **5o**. Reaction time: 50 min. Colourless solid (92%). M.p. 162 – 3 °C. ^{1}H NMR ($CDCl_3$). δ_{ppm}: 1.56 (d, 7.0 Hz, 3H); 2.55 (s, 3H); 3.16 (s, 3H); 3.45 (s, 3H); 4.91 (q, 7.0 Hz, 1H); 4.95 (d, 17.5 Hz, 1H); 5.01 (d, 17.5 Hz, 1H); 7.17 (pt, 7.2 Hz, 1H); 7.23–7.35 (m, 4H). ^{13}C NMR ($CDCl_3$). δ_{ppm}: 14.0 p; 14.6 p; 30.1 p; 31.2 p; 47.4 s; 54.0 t; 93.2 q; 125.6 t; 126.2 t; 128.8 t; 142.7 q; 159.2 q; 159.9 q; 161.9 q; 168.8 q. IR (KBr) ν (cm^{-1}): 3054 (w); 3007 (w); 2925 (m, b); 2857 (m); 1683 (s); 1652 (s, b); 1597 (s); 1545 (s, b); 1492 (m). MS (70 eV) *m/z* (%): 344 (M^+, 29); 301 (18); 239 (22); 223 (30); 209 (100); 178 (10); 88 (25). HR MS: calc for $C_{17}H_{20}N_4O_2S$ 344.1307; found 344.1314.

Crystal data for **11f** were deposited at CCDC with reference CCDC 1,422,147: Chemical formula $C_{17}H_{20}N_4O_2S$, M_r 344.13, Monoclinic, *C2/c*, 120 K, cell dimensions *a, b, c* (Å) 19.7765 (14), 12.7797 (17), 13.8467 (14); α, β, γ (°) 90, 110.854 (8), 90. *V* (Å^3) 3270.3 (6), *Z* = 8, *F*(000) = 1456, D_x (Mg m^{-3}) = 1.399, Mo *K*α, μ (mm^{-1}) = 0.216, Crystal size (mm) = 0.25 × 0.20 × 0.18. Data collection: Diffractometer KappaCCD diffractometer, Monochromator graphite, CCD rotation images, thick slices φ & θ scans, absorption correction *SADABS* 2.10, *T*min, *T*max 0.6446, 0.7456. No. of measured, independent and observed [$I > 2\sigma(I)$] reflections 26,146, 3738, 2619, *R*int = 0.053, θ values (°): θmax = 27.5, θmin = 3.1; Range $h = -25 \rightarrow 25$, $k = -16 \rightarrow 16$, $l = -17 \rightarrow 17$, Refinement on $F2{:}R[F2 > 2\sigma(F2)] = 0.043$, $wR(F2) = 0.092$, $S = 1.07$. No. of reflections 3738, No. of parameters 221, No. of restraints 0. Weighting scheme: $w = 1/\sigma^2(F_o^2) + (0.0365P)^2 + 3.3545P$ where $P = (F_o^2 + 2F_c^2)/3$. $(\Delta/\sigma) < 0.001$, $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3}) 0.26, −0.27.

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Appendix A. Supplementary material

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